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ANNUAL ORATION

SAFE MANAGEMENT OF FRACTURES*

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WORCESTER, MASSACHUSETTS

A REVIEW of the titles of previous orations indicates that fractures were first discussed by an orator of this society in 1840. The speaker was A. L. Pierson, M.D. His must have been a sturdy audience if he read all that was printed, amounting to seventy-three pages of narrative and twenty-four additional pages combining case reports and fracture statistics of the period 1821 to 1840 from the Massachusetts General Hospital.

Referring to treatment, the speaker made the following remarks:

> It is the duty of every good surgeon at all times to wait upon nature. But more especially is this true of the treatment of fracture, where all that art can do is to effect the coaptation of divided parts and guard against accidents. The rest is purely a natural process, which receives no aid from art.

(The late Dr. Nathaniel Allison, of Boston, discussing a very lengthy paper along similar lines, confined his remarks to the single phrase "Ain't Nature grand?")

For intracapsular fracture of the hip Dr. Pierson recommended following the advice of Sir Astley Cooper that "the patient be made as comfortable as can be and the fracture left to its fate." The speaker concluded "I have thus completed a practical sketch of the subject of fractures, the difficulty of compressing which into a moderate space I did not at first appreciate; and I should much regret if, in laboring to be brief, I have become obscure."

Five years later, Orator William J. Walker, M.D., presented an address entitled "On the Treatment of Compound and Complicated Fractures." This material also was published, the narrative filling forty-four pages supplemented by fifty-six pages of finely printed case histories, a total of one hundred pages, or more than three hours' reading time.

In the fifth century before Christ, Greek physicians, among them "that astonishing old genius Hippocrates," were using rest, reduction by traction and external splinting in the management of fractures.

In the course of a sojourn in Asia Minor some thirty years ago, I heard several times of a curious method used by desert Arabs for treatment of fractures of the lower extremity. I have not seen it recorded. The patient remains where he fell. A hole of proper dimensions is dug in the sand beneath his buttocks, and clothing between it and the excretory apertures is removed. The injured extremity is cradled comfortably. If the digger has made a nice estimate, the fracture should be healed and the hole filled at about the same time.

There was nothing in either of the orations of a century ago to suggest remarkable improvement over much older technics.

A CENTURY OF PROGRESS

For a hundred and five years nothing more has been heard about fractures from an orator of this society. I do not propose to fill the gap in detail but shall mention a few facts, names and dates for orientation.

Ether was first used in public as an anesthetic for an operation on October 16, 1846, at the Massachusetts General Hospital. Between 1850 and 1860 skin traction in the form of Buck's extension, and plaster of Paris for splinting, came into fairly common use. In 1867 Lister's monograph on antisepsis, much of it based on study of compound fractures, was published. In 1888 surgical instruments were sterilized by boiling, and the era of aseptic surgery had opened. Hugh Owen Thomas (1843 to 1891) devised the splint that bears his name, and many others. Roentgen described x-rays in 1896. Great improvement in equipment has been made in recent years. That boon to cartoonists, the frame

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over the bed, to support balanced traction, is called the Balkan frame because it appeared during the Balkan War of 1903. Skeletal traction by means of the Steinmann pin or Kirschner wire dates from 1909. In 1910 Sir Arbuthnot Lane came to this country to talk about open reduction and internal fixation of fractured long bones by means of the Lane plate. F. H. Albee, who devised a bone-grafting operation for Pott's disease in 1911, found hand tool methods crude, requiring too much time, tiring the surgeon and unnecessarily shocking the patient. He devised an electric operating set, run by a small universal motor. "Splint 'em where they lie" was a slogan of World War I. Thereafter, to the present day, the Committee on Fractures of the American College of Surgeons has worked unceasingly to improve the transportation of injured persons, particularly of those with fractures. During and after World War I surgical shock was studied intensively. Means to combat it were developed and improved in World War II. The Carrell–Dakin method of managing compound fracture had a brief vogue, followed shortly by the Orr method, popularized later by Trueta in the Spanish Civil War and used widely everywhere between the two world wars. In the ten years following War I, Böhler, of Vienna, had a good bit to say about management of fractures, recommending, among other changes, the unpadded cast. In 1924 Russell described his widely used system of traction. Effective chemotherapy began with sulfonamides in 1935. Penicillin, streptomycin and aureomycin followed. Great strides in the art and science of anesthesia have been made. Spinal anesthesia, attempted sporadically since the turn of the century, has finally attained a secure place.

Twenty-five or thirty years ago much of the metal used for internal fixation of fractures came from the hardware store. Broken plates, loose and broken screws and unfortunate consequences were common. From that unhappy day we have come far. Before he left the Massachusetts General Hospital about fifteen years ago for an assignment in New York, Philip D. Wilson had enlisted the interest of the National Bureau of Standards in our hardware problems. Venable and Stuck soon afterward reported that electrolysis was "the controlling factor in the use of metals in treating fractures."

A paper by Leonard T. Peterson entitled "Fixation of Bones by Plates and Screws" in the *Journal of Bone and Joint Surgery* for April, 1947, summarized knowledge and practice up to date.

To me personally, the most stimulating paper of this period was that of Smith-Petersen, Cave and Van Gorder, published in 1931 in the *Archives of Surgery*, on the treatment of intracapsular fractures of the hip by internal fixation. Each winter before that since I had been in practice, I had looked with dismay at a ward full of about thirty old women with broken hips, buried in plaster spicas. They were a miserable, unhappy lot. Any measure to improve their condition was welcome. Dealing, as we did, largely with patients from the lowest economic and social levels, in the wards of a municipal hospital, the operation as proposed was too formidable for safety. It soon occurred to me, as it did to others, that if the operation could be made simpler and safer, much suffering might be eliminated. My contribution was "Blind Nailing," presented in 1934 to the New England Surgical Society and in 1935 to the American Academy of Orthopaedic Surgeons. Several other surgeons had previously described methods simpler and safer than the original. Open reduction, with its attendant hazards, was quickly supplanted by blind nailing, by that and other names. Internal fixation of the fractured femoral neck by one instrument or another, without open reduction in nearly all cases, is now standard procedure among fracture surgeons.

External skeletal fixation in the treatment of fractures was tried and discredited for the first time nearly a hundred years ago.

In 1921, here in Boston, where he was guest of honor at a meeting of the American Orthopaedic Association, Vittorio Putti, of Bologna, one of the world's great orthopedic surgeons, described informally the apparatus he was using for leg lengthening. It was a modification of the method previously employed by his chief, Codivilla. In the same year a paper by Putti, reporting 10 cases, appeared in the *Journal of the American Medical Association*. Not many years afterward, Abbott modified Putti's apparatus, increasing the number of transfixion pins from two to four. Anderson, Stader (a veterinarian) and Haynes, still later, applied the Putti and Abbott principles to the treatment of fractures, each devising modifications of the Abbott leg-lengthening apparatus. All these have appeared in the last fifteen or sixteen years. Stader's splint, devised for animals, particularly dogs, was adapted to human beings and used in a considerable series of well managed fractures at Bellevue Hospital shortly before the United States entered World War II. The war provided a tremendous opportunity to try again on a large scale the methods of external skeletal fixation. Its scope and particularly the Navy's participation in it required that fractures, especially those occurring at sea, be treated under unusual conditions and, unfortunately, often by physicians with little previous experience. In the unusual circumstances of naval warfare external skeletal-fixation splints were widely used where simpler and safer methods might have been chosen under different conditions.

Intramedullary fixation in the treatment of long-bone fractures came to public attention in this country through a somewhat dramatic story in a national magazine about 1942. An American soldier, released from a German prison camp after

having sustained a fracture of the femur, came home with the fixation instrument in the bone. He had been treated without a cast or other external splint and had been walking since the operation. Küntscher had described the method in Germany in 1940 and devised the rod that bears his name. The medical literature reveals that intramedullary fixation of the clavicle had been carried out in France as long as forty years before. After the war the method was taken up in this country. MacAusland reported 7 cases in *Surgery, Gynecology and Obstetrics* in January, 1947, and further reports have appeared in abundance.

Among the technical exhibits at medical meetings, the tools are displayed and attract maximum attention. At the moment, this is the spectacular way of treating a fracture.

Management Today

The methods of fracture management a century ago have been referred to and compared briefly with primitive practice. Differences are not remarkable. Some of the enormous contributions of the last century have been mentioned. No doubt many others equally deserving have been omitted.

Here now is our overflowing kit of tools. How shall we use them in the best interest of the patient? Do we need less knowledge of the basic sciences — less skill, judgment and experience? Do our newly acquired diagnostic aids of the laboratory and the x-ray department make history, physical examination and the use of our senses unnecessary? Does each new surgical gadget render its predecessor obsolete? Does the gun replace the man behind it?

The treatment of fractures has become more exacting and complex than ever. With new tools have come new standards. Our end results are seen and critically examined not only in the hospital and by the attending surgeon but also by his professional associates and, in cases involving workmen's compensation or tort, by other physicians, lawyers, the court and often the patient himself. The management of fractures now involves so much responsibility and perhaps risk of malpractice suit that many physicians prefer not to become involved.

It is clear that the trend is toward more and more surgical management. Is that good? Surely it should never be said, paraphrasing Bick, that the only excuse for surgery is the surgeon's enthusiastic desire to practice his craft. I recently heard a young surgeon's mother say of her son "he is only happy when his hands are in someone's belly." Also, recently, I heard of a resident, nearly ready to start practice after many years of training in surgery, who upon reporting to his superior on a child with fractures of both bones of the forearm and being asked what he would do about it, replied that the only treatment he would be competent to carry out would be open reduction and internal fixation of each bone. Sir Robert Jones said that of many thousands of fractures of both forearm bones, he could remember not more than a dozen on which he had to operate.

Is it not a responsibility of those who teach fracture management to resist eager surgeons, reckless enthusiasts and the pressure of instrument salesmen?

The treatment of fractures is not limited to a few experts. It has been estimated that the number of fractures occurring in this country annually now is between 1,000,000 and 1,500,000. If the patient will permit it, any physician with a license to practice may treat a fracture, any fracture, and by any method he sees fit to use.

Let us not forget that open management of any type is more hazardous than closed and that the consequences of error may be tragic.

Who knows how many patients with simple fractures of the leg, treated by open reduction and internal fixation, have or have had chronic osteomyelitis, delayed or absent union, stiff or partially stiff and painful ankles? The large clinics report some figures, but everybody is doing it. What are the average man's statistics?

Nor are infection and osteomyelitis the only hazards. Multiple wires in the foot or hand may produce exceedingly painful and disabling osteoporosis, without infection. Nonunion may result from distraction, easily accomplished by direct traction on bone.

Treatment of a fractured neck of the femur by internal fixation is well established and without doubt represents one of the striking advances in the field of fracture management. Before the discovery of this method and under the most favorable conditions, fracture of the neck of the femur healed in approximately 3 cases out of 10 — under average conditions, in probably not more than 1 in 10 cases. Internal fixation, well done, improved the incidence of union to 75 per cent.

This, then, is a method of operative treatment that is justified in capable hands. It is the safest method for handling this particular injury. The penalty for error averages less than that for closed methods.

Does that hold true, however, for intertrochanteric fractures? I mean the fragmented type, not the fracture close to the base of the neck with a solid trochanteric mass that can be nailed in the way that a fracture of the femoral neck can be nailed. By any method of treatment nonunion is practically unknown. The difficulty here is to avoid shortening.

Open reduction and internal fixation of this fracture represent much more of an undertaking for patient and doctor than the same treatment of a fracture of the femoral neck. The patient averages nearly ten years older, his degenerative processes are farther advanced, his activities were probably restricted before the fracture occurred, his bones are brittle and his fracture is in multiple fragments,

some of which may not have been demonstrated on the preoperative x-ray examination.

To reassemble this jigsaw puzzle of broken bones in a field of blood requires a large incision, liberal instrumentation and a formidable mass of hardware. Statistics have appeared from a few large fracture clinics claiming that it is the best method. It may be, in some circumstances, but what of the cases not reported? Let us not forget that many an excellent result has been obtained in the past by carefully tended skin traction and good nursing. That method is as good now as it ever was. The management of an elderly patient in traction is not spectacular but it is fairly safe.

Let this not be a decision in which the excuse for surgery is the enthusiastic desire on the part of the surgeon to practice his craft.

Delayed Reduction

The average patient thinks of a fracture as an emergency. He heads straight for the nearest hospital and often prefers the resident on the job to the visiting man who will be there in the morning.

The method of delayed reduction practiced by J. R. Moore at Temple University Hospital for eight years and in more than 7000 cases should be better known. His plan for handling fractures is as follows:

> In the first place, all patients are examined immediately for nerve and vessel injury and for such complications as head, spinal-cord and internal injuries. The treatment of these major problems is instituted immediately by the department concerned.
>
> Secondly, all fractures of the long bones are immobilized immediately in plaster-of-Paris splints that routinely include the joint above and the joint below.
>
> Thirdly, roentgenograms are taken at the convenience of the roentgenographic department, either immediately or on the following day.
>
> Finally, one day a week is set aside for the reduction of fractures.

In reporting upon this method Moore concluded as follows:

> The reduction of fractures may be delayed. The ideal time for delayed reduction is between the fourth and eleventh day. Complete immobilization in plaster should precede delayed reduction. Compound fractures [with exceptions which he noted], simple dislocations, compound dislocations and fractures complicated by nerve or vessel injury should be regarded as emergencies. The time required for repair in the group of delayed reductions would seem to date from the time of fracture, rather than from the time of reduction, since additional delay was not observed. Union and function appear to be unhampered. Delayed reduction provides the opportunity for excellent teamwork. The best trained individuals are readily available for all purposes. The patient is adequately prepared for anesthesia. . . . If teams which provide well-trained supervision are available for immediate reduction, immediate reduction should be done. In localities where well-trained supervision is not at hand, it would appear that delayed reduction is by far the better procedure. . . . A well-supervised delayed reduction is better than a poorly supervised immediate reduction.

Intramedullary Fixation

At a medical meeting here five months ago a well informed and very enthusiastic young man spoke about intramedullary fixation. He described many patients he had managed by this method. He had treated each long bone, including phalanx, metacarpal, radius, ulna, humerus, clavicle, femur, tibia, fibula and metatarsal. The nails were introduced by open operation. He stated that intramedullary canals vary in diameter from patient to patient, from bone to bone and in different segments of the same bone. He also said that the nails often become incarcerated so that they can neither be driven in farther nor extracted, without special equipment and great difficulty. He added that at least $600 worth of nails of various sizes and shapes should be in any beginner's kit.

Three months ago, among the technical exhibits at the meeting of the American Academy of Orthopaedic Surgeons in New York, were several instruments for intramedullary fixation and tools ancillary thereto. An "intramedullary outfit" was shown.

The immediate future looks ominous. The havoc wrought among servicemen of World War II with instruments for external skeletal fixation may be the lot of civilians with intramedullary fixation.

The method may have some merit. The Fracture Committee of the American Academy of Orthopaedic Surgeons reported upon it in February, 1950. Dr. Herman F. Johnson, committee chairman, was kind enough to lend me a copy of the report, as yet unpublished. The following is quoted:

> For those who may be on the fence about proceeding with this technique for fresh fractures of the femur, we offer the following statement: given the proper indication, intramedullary fixation is the most effective form of therapy for many fractures of the shaft of the femur. That statement must now be diluted a bit. This technique if applied to improperly selected cases, or if inefficiently or unskillfully carried out, offers more intriguing possibilities of trouble than any other. Most of us have had at least one unhappy, though not necessarily catastrophic experience.
>
> Probably the most common error consists of inserting a pin that is either too long, too short, too big or too small. A pin tightly lodged or impinged in an intramedullary canal may develop into a very chastening experience. A short or loose pin provides inadequate fixation. For these reasons, intramedullary fixation of the femur necessitates considerable planning, pre-operatively. There is no formula for the size of a canal in relation to the length of the bone.
>
> Local complications are bound to occur in this technique, particularly bent pins, migration of pins, distraction of fragments, insecure or incomplete fixation, and the complications that may be attendant upon any technique that requires exposure of bone.

The entire report is too long for quotation here. No bone but the femur was reported upon. In

general, the authors, expert orthopedic surgeons, appear to view the method with some favor. For me, their recital of errors and complications dilutes this "most effective form of therapy for many fractures of the shaft of the femur" considerably more than "a bit."

If it can be safely used to ease the pain and assure a comfortable outcome in injuries hitherto difficult to manage, such as pathologic fracture of the femur, and by surgeons who are willing to learn in detail and in advance the anatomic vagaries of the intramedullary canal in old and young, long and short, knock-kneed and bowlegged; and who will report in detail and with complete candor, something may eventually come of the method. It should not be regarded as an opportunity for reckless enthusiasts who like to practice their craft.

Conclusion

In conclusion, the increasing trend toward surgical management of fractures is recognized. Three major surgical means are available to all. Best established is open reduction and internal fixation or, in occasional situations such as the femoral neck, closed reduction and internal fixation. External skeletal fixation has been mentioned. Last and presently most glamorous is the method of intramedullary fixation.

In a presidential address to the American Academy of Orthopaedic Surgeons, Dr. A. B. Gill, of Philadelphia, remarked, in substance, that to treat all fractures by any special apparatus as though that supplanted use of head and hands is both ridiculous and futile. He also advised the study of principles rather than methods and added "a mind that grasps principles will devise its own methods." In Campbell's *Textbook of Operative Orthopedics* is the statement that "the majority of fractures may be reduced by closed methods; surgery should never be recommended unless definitely warranted."

Sir Robert Jones, the most revered teacher and practitioner of orthopedic surgery of this century, stated that nonoperative methods give a high percentage of good results even when exact reposition is not obtained. He said also that nonoperative treatment by a surgeon who understands body mechanics is always more successful than operative treatment by a surgeon who neither knows nor cares much about the functions of a limb. Advice such as this is too good to be forgotten.

To the patient the major calamity associated with a broken bone is that he has lost its function. The major job of the doctor is to restore that function quickly and completely if he can but, by all means, safely.

In writing the foregoing, I have no doubt employed phrases or even sentences, some recently seen, others long remembered, the sources of which are forgotten. Obligation to the authors is acknowledged.

For the honor and privilege of delivering the one hundred and forty-sixth oration, I am deeply grateful.

UROLOGIC ASPECTS OF RADICAL PELVIC SURGERY*

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BOSTON

IN JULY, 1948, Brunschwig[1] reported his experience with ultraradical surgery for advanced pelvic carcinoma. Since that time considerable interest has been created in the radical surgical treatment of malignant lesions of the pelvic viscera previously regarded as beyond the scope of effective treatment.

Our own series began in December, 1947, on material available from the tumor clinics of the Massachusetts General, Palmer Memorial and Pondville hospitals. The program was undertaken in an attempt to find out whether this type of surgery had anything to offer, whether the patients could survive the operation, whether the patients so treated could live happy, useful lives and finally whether any permanent salvage could be expected. Now, after twenty-one months, although this work is definitely in the experimental stage, enough is known to allow us to state that the patients can survive the operation and live happy, useful lives thereafter. Nine of 29 patients are living twelve to twenty-one months after the operation.

The mortality following this procedure is formidable. Rather than choose an arbitrary period of a month to represent the time element within which the patient's death may be attributed to the operation, we have elected to regard the death as operative if the patient failed to be discharged home from the hospital. With the use of this criterion the operative mortality is 35 per cent. It is believed that this figure in no way represents the expectancy, for improvement can be anticipated as improved technic and greater familiarity with the problems encountered in the postoperative period become better known. It must be remembered that these patients were offered surgery only after complete radiation had resulted in failure and all further treatment was regarded as futile. The mortality will therefore always be high. It has become obvious, however, that aside from the immediate technical difficulties of the operation, the chief problem has been the management of the urinary-tract complications.

The purpose of this communication is to report our experience in the handling of these urologic problems in the hope that others may profit from our experience.

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OPERATION

It may be well at the outset to define what is meant by ultraradical surgery. In addition to a bilateral pelvic lymphadenectomy, an abdominoperineal resection of the uterus, bladder, rectum, vagina and vulva is performed in one operation. Excretion from the urinary and gastrointestinal tracts is established by transplantation of the ureters into a sigmoid colostomy. Under certain conditions the ureters may be brought out through the skin to function as cutaneous ureterostomies. At times, depending on the extent of the disease, it is possible to spare either the rectum or the bladder.

Of this group of 29 patients only those are included who have had a cystectomy as part of the operative procedure. In 25 cases the complete operation was performed, whereas the rectum was preserved in 4. Table 1 summarizes the methods employed to provide urinary drainage. Table 2 lists all the cases, the pathological diagnoses, the preoperative evaluation of the upper urinary tract, the types of operation performed, the complications, the secondary operations and the results.

TABLE 1. *Summary of Original Means Employed in Providing for Diversion of Urine.*

PROCEDURE		No. OF CASES
Bilateral ureterosigmoidostomy		19
Into intact sigmoid	16	
Into isolated sigmoid loop	3	
Unilateral ureterosigmoidostomy		3
With ligation of opposite ureter	2	
With preliminary nephrostomy on opposite side	1	
Bilateral cutaneous ureterostomy		4
Unilateral cutaneous ureterostomy:		
With ligation of contralateral ureter		3
Total		29

PREOPERATIVE UROLOGIC STATUS

In addition to extensive chemical blood studies to determine kidney function, a preoperative urologic examination was made in each case. Intravenous urograms and cystoscopy were performed to determine as far as possible the degree of extension of the disease to the urethra, bladder and lower ureter. Direct involvement of the urethra and bladder were infrequently encountered. On the other hand, disease of the upper urinary tract secondary to infection and varying degrees of ureteral obstruction were commonly noted. The preoperative urinary findings are presented in Table 3.

TABLE 2. *Urologic Management in 29 Patients with Total or Partial Excision of Pelvic Viscera.*

CASE NO.	AGE	DIAGNOSIS	STATUS OF URINARY TRACT	TREATMENT OF URETERS	SECONDARY OPERATION	COMPLICATIONS	RESULT
	yr.						
1	61	Carcinoma of cervix	Nonfunctioning left kidney	Skin ureterostomy on right; ligation of left ureter.	None	None	Death from recurrence after 9 mo.
2	40	Leiomyosarcoma of vagina	Normal	Bilateral ureterosigmoidostomy into blind sigmoid pouch	Excision of pouch; ureters reimplanted into sigmoid.	Perineal urinary fecal fistula; oliguria.	Death in 6 mo.
3	38	Carcinoma of cervix	Bilateral hydroureter and hydronephrosis	Bilateral skin ureterostomy	None	Retraction of right ureterostomy; oliguria; uremia.	Death in 7 days
4	—	—	Normal	Bilateral ureterosigmoidostomy into blind sigmoid pouch	Right nephrostomy, with decapsulation	Anuria, uremia and sepsis	Death in 2 wk. from uremia and sepsis
5	30	Carcinoma of cervix (retained rectum)	Normal	Bilateral ureterosigmoidostomy	Transverse colostomy	Perineal urinary fecal fistula	Death from gastrointestinal hemorrhage in 5 mo.
6	62	Adenoacanthoma of uterus	Normal	Bilateral ureterosigmoidostomy	None	None	Patient living and well 20 mo. after operation
7	43	Carcinoma of cervix	Left hydronephrosis and hydroureter	Bilateral ureterosigmoidostomy	Right pyelotomy and nephrostomy 1 yr. after operation	Bilateral renal calculi 1 yr. after operation	Patient living and well 20 mo. after operation
8	48	—	Normal	Bilateral ureterosigmoidostomy	None	Transient oliguria	Death from recurrence in 4½ mo.
9	60	Adenocarcinoma of uterus	Normal	Bilateral ureterosigmoidostomy into defunctioned sigmoid loop	Left nephrectomy; right nephrostomy.	Malfunction of transplants; pyelonephritis.	Patient living and well 17 mo. after operation
10	52	Carcinoma of cervix	Nonfunctioning left kidney	Bilateral ureterosigmoidostomy	None	Operative death	—
11	44	Carcinoma of cervix	Nonfunctioning right kidney	Left ureterosigmoidostomy; ligation of right ureter.	None	Operative death	—
12	41	Carcinoma of cervix	Normal	Bilateral ureterosigmoidostomy	None	Transient perineal urinary fecal fistula (healed spontaneously)	Patient living and well 15 mo. after operation
13	38	Carcinoma of cervix (rectum retained)	Left cortical atrophy and chronic pyelonephritis	Bilateral ureterosigmoidostomy	Bilateral skin ureterostomy	Malfunction of bowel transplants; sepsis.	Patient living and well 15 mo. after operation
14	—	Carcinoma of cervix	Normal	Bilateral ureterosigmoidostomy	None	None	Patient living and well 19 mo. after operation
15	38	Carcinoma of cervix	Nonfunctioning right kidney	Bilateral ureterosigmoidostomy	Left skin ureterostomy	Oliguria, sepsis and malfunction of transplants	Death in 1½ mo.
16	53	Carcinoma of cervix (rectum retained)	Left chronic pyelonephritis	Bilateral ureterosigmoidostomy	None	Uremia; sepsis; right transplant detached.	Death in 10 days
17	53	Adenoacanthoma of cervix	Normal	Bilateral ureterosigmoidostomy	None	Uremia; sepsis; right transplant detached.	Death in 1 mo.
18	61	Radiation fibrosis of vagina	Normal	Bilateral ureterosigmoidostomy	Left nephrectomy, 7 mo. after operation	Bilateral renal calculi 7 mo. after operation	Patient living and well 12 mo. after operation
19	56	Carcinoma of cervix	Nonfunctioning left kidney	Right ureterosigmoidostomy; ligation of left ureter.	None	Pyelonephritis	Patient living and well 9 mo. after operation
20	—	Carcinoma of cervix	Nonfunctioning right kidney	Bilateral skin ureterostomy	None	Oliguria, sepsis and uremia	Death in 1 mo.
21	43	Carcinoma of cervix	Normal	Bilateral skin ureterostomy	None	None	Death from recurrence in 10 mo.
22	41	Carcinoma of cervix	Normal	Bilateral ureterosigmoidostomy	None	Transient oliguria	Patient living and well 9 mo. after operation
23	38	Adenocarcinoma (source undetermined)	Right hydronephrosis; nonfunctioning left kidney.	Preliminary right skin ureterostomy; ligation of left ureter.	None	None	Death from recurrence in 6 mo.
24	34	Carcinoma of cervix	Right hydroureter and slight hydronephrosis	Bilateral skin ureterostomy	None	Transient pyelonephritis	Patient living and well 7 mo. after operation
25	53	Carcinoma of cervix	Bilateral hydronephrosis	Preliminary right nephrostomy; ligation of right ureter; left ureterosigmoidostomy.	None	Transient perineal fecal fistula	Patient living and well 7 mo. after operation
26	54	Carcinoma of cervix	Hypoplastic, nonfunctioning right kidney	Left skin ureterostomy	None	Uremia and lower-nephron nephrosis	Death from complication
27	42	Carcinoma of cervix	Normal	Bilateral ureterosigmoidostomy	Transverse colostomy	Perineal urinary fecal fistula; oliguria	Patient living and well 5 mo. after operation
28	45	Carcinoma of cervix	Normal	Bilateral ureterosigmoidostomy	None	Transient perineal urinary fistula	Patient living and well 5 mo. after operation
29	—	Carcinoma of cervix	Normal	Bilateral ureterosigmoidostomy	Left nephrostomy	Uremia and lower-nephron nephrosis	Death from complications

Despite the fact that half the 29 patients had varying degrees of renal damage before operation, no patient was refused operation on the basis of the preoperative urologic status. However, ureteroenterostomy was not chosen as the means of diverting the urinary stream when the renal reserve was considered to be minimal.

Cases Treated Primarily by Ureteroenterostomy

Method of Transplant

There are a variety of methods of transplanting the ureters into the bowel. The most widely known is that of Coffey,[2] who employed the principle of oblique transplantation. Nesbit[3] and Cordonnier[4] have recently advocated a direct mucosa-to-mucosa anastomosis. For the most part the method utilized in this series was a simple stab wound. After slitting or "fish mouthing" of the distal centimeter of the ureter, direct transplantation is accomplished by introducing the ureter through a small stab wound and fixing the cut end within the lumen of the bowel by a single mattress suture, supplemented by two additional sutures through the serosa of the bowel to bring it snugly about the ureter. Occasionally, an additional fixation suture is placed in the adventitia of the ureter and the serosa of the bowel to anchor the ureter more securely.

Table 3. *Summary of Preoperative State of Upper Urinary Tract in 29 Patients.*

State of Upper Urinary Tract	No. of Cases
Normal intravenous urograms	14
Unilateral hypoplastic kidney	1
Bilateral chronic pyelonephritis	1
Unilateral pyelonephritis	1
Unilateral hydroureter and hydronephrosis	2
Bilateral hydroureter and hydronephrosis	3
Unilateral nonfunctioning kidney	7

Some form of ureteroenterostomy was performed in 22 of the 29 cases. In 19 of these, both ureters were transplanted into the bowel. Except for 1 case the portion of the bowel chosen was the sigmoid. In this case (Case 7) operative necessity demanded insertion of the right ureter in the cecum; it is interesting to note that a kidney stone developed one year after operation. In 3 cases a transverse colostomy was performed, and the ureters were transplanted into an isolated loop of sigmoid.

In the 3 remaining cases only one ureter was implanted in the sigmoid. The opposite ureter was ligated for a number of different reasons. Case 26 presented a hypoplastic kidney. Atrophy from a long-standing hydronephrosis had reduced kidney function in Case 11. Because of pyelonephritis, secondary to obstruction, a nephrostomy with ligation of the upper ureter preceded the evisceration procedure (Case 25).

Urologic Complications

The urologic complications from this procedure fell into three classifications: oliguria and anuria secondary to shock or transfusion reactions; fecal urinary fistulas; and oliguria or anuria with hydronephrosis and pyelonephritis secondary to poorly functioning ureteroenterostomies.

Oliguria and anuria from lower-nephron nephrosis. In the type of ureterointestinal anastomosis employed a depressed urinary excretion was a common finding. Oliguria usually persists for four or five days. In the face of a mounting nonprotein nitrogen one must be ready to perform a temporary nephrostomy lest renal function further deteriorate from back pressure and hydronephrosis. It is very difficult to differentiate impaired renal function due to lower-nephron nephrosis from that secondary to ureteral obstruction at the site of the anastomosis.

There were 7 deaths among the 22 patients who had ureterosigmoid anastomoses. Four of these died from kidney damage secondary to the trauma of the operation. Early in the series 2 patients died from the shock of the operative procedure (Cases 10 and 11). The remaining 2 died early in the postoperative period from lower-nephron nephrosis (Cases 4 and 29). Unilateral nephrostomy and decapsulation were attempted in Case 4 without improvement. A unilateral nephrostomy alone did not alter the course in Case 29. It is possible that too much blood was given in replacement of actual blood loss, thereby contributing to lower-nephron nephrosis. The amount of actual blood loss is a great variable. Certainly, with increasing familiarity with the operative procedure the amount has been materially reduced. In the more recent cases the actual blood loss has been measured, and blood replacement regulated. Nevertheless, a fatal lower-nephron nephrosis developed in 1 of these patients. It must be continually kept in mind that one is dealing with kidneys already damaged, in anticipation of further insult. Every effort must be made to spare the kidneys.

Obstructive ureterointestinal anastomoses. The remaining 3 patients of the 7 who died succumbed to sepsis and pyelonephritis (Cases 15, 16 and 17) as a direct result of poorly functioning ureteroenterostomies. Half the complications may be directly traceable to poorly functioning ureterointestinal anastomoses. Seven of the 22 patients had a relatively uncomplicated convalescence.

In the presence of an obstructive anastomosis the problems of management become complicated.

A *cutaneous ureterostomy* was performed too late to influence the terminal course of 1 patient dying of sepsis and pyelonephritis (Case 15). On the other hand *bilateral cutaneous ureterostomy* salvaged a patient on whom an ill considered bilateral ureterosigmoidostomy had been performed in the face of preoperative evidence of chronic bilateral pyelo-

nephritis. In certain cases it has been possible to *catheterize the ureters through the colostomy* by means of a cystoscope. Usually, only the right ureter can be visualized. This is a most useful procedure when there is doubt whether the oliguria is secondary to a lower-nephron syndrome or whether the cause is primarily obstructive. The procedure is not without the element of possible danger, inasmuch as the site of the anastomosis may be damaged by manipulation with the cystoscope or catheter. *Nephrostomy* as an emergency procedure may tide the patient over the immediate crucial period. The value of nephrostomy was well demonstrated in 1 case, in which a bilateral obstruction developed in a ureterointestinal transplant into a defunctioned sigmoid loop. An emergency right nephrostomy provided immediate salvage. Subsequently, an attempted left cutaneous ureterostomy failed, and a left nephrectomy was performed. Despite the fact that this patient's only urinary outlet is from the right nephrostomy she has continued in fair health and is working in a factory twenty-one months after operation.

Abdominoperineal fistulas. Six of the 22 patients sustained perineal or abdominoperineal urinary fecal fistulas, which were due either to leakage at the sites of the ureterointestinal anastomoses or to defect in the bowel below the site of the implantation. In 3 patients (Cases 12, 25 and 28) the fistulas healed spontaneously. A proximal colostomy designed to divert the fecal flow failed to influence healing in Cases 5 and 27, since the fistulas persisted. An attempted retransplant of the ureters higher up in the sigmoid proved only partially successful, for the patient died of pyelonephritis and late recurrence of a leiomyosarcoma six months later.

In a review of the complications from this radical procedure it is at once evident that the problem is almost entirely one of providing satisfactory urinary drainage. *Seven of the 22 patients had an uncomplicated convalescence.* Eight patients with urinary complications recovered. The morbidity and mortality, however, are directly traceable to the success or failure in providing adequate drainage.

Late Results

Seven of the 22 patients failed to leave the hospital, giving a mortality rate of 31.8 per cent. Fifteen of the 22 lived, or are living at present, five to twenty-one months after operation. Nine have survived for twelve to twenty-one months. All these patients have resumed their previous occupations and appear to be happy in their existence. Twelve are alive at present.

There have been 3 deaths among patients leaving the hospital. Two died of late recurrence eight and ten months after operation. The third patient (Case 5) died from a massive gastrointestinal hemorrhage after five months. No source for the hemorrhage was disclosed at autopsy. It was encouraging to note that there was no evidence of recurrent disease.

In 2 patients bilateral renal calculi subsequently developed. A pyelolithotomy and permanent nephrostomy was performed in 1 (Case 7) a year after operation. The other patient (Case 18) required a left nephrectomy seven months later. The function of the remaining kidney, in spite of a small stone, has remained satisfactory.

Two of the patients on whom a secondary operation proved necessary during the convalescence for relief of obstruction at the site of the ureterointestinal anastomosis have done well. For the entire group the subsequent intravenous urograms are rarely normal. The results may be classified as good to poor.

Cutaneous Ureterostomy

In the group of 29 patients exposed to radical pelvic operation including a cystectomy, 7 had a cutaneous ureterostomy as a means of providing urinary excretion. This procedure was chosen in most cases because of the preoperative finding of severely damaged kidneys. It seemed more logical to protect such a kidney from possible further damage incident to ascending infection that might follow ureterointestinal anastomosis.

Bilateral cutaneous ureterostomy was performed in 4 cases, and in the remaining 3, one ureter was brought to the skin and the other ureter ligated because of an associated nonfunctioning kidney. It is of interest that in 2 cases kidneys that appeared nonfunctioning on intravenous urograms performed four months previously and checked before operation were completely restored after cutaneous ureterostomy.

Three patients (Cases 2, 20 and 26) failed to leave the hospital. The cause of death in 2 (Cases 2 and 26) proved to be lower-nephron nephrosis. The third patient (Case 20) died of uremia and sepsis directly attributable to a maladjusted ureterostomy.

Late Results

Four patients of the 7 with cutaneous ureterostomy recovered and left the hospital after a relatively short hospital stay. Three have since died of recurrence — 2 at six months, and 1 at ten months. None had urinary-tract complications, and all had returned to their former occupations, one as a secretary. The sole surviving patient in this group lives comfortably in good health, seven months after operation.

Discussion

The operative and postoperative mortality from this radical procedure has been high. It must be kept in mind, however, that these patients had all received extensive radiation previously and had been regarded as beyond help from any further

radiation. The immediate mortality appears in large part to be due to lower-nephron nephrosis, 6 patients dying from this syndrome. The proper management of blood and fluid replacement is a formidable one.

The problem of postoperative management, on the other hand, depends directly on the maintenance of a proper urinary flow. The most important consideration, then, is to reduce the number of urologic complications due to obstruction, oliguria and pyelonephritis and to avoid the development of urinary fecal fistulas. Nearly all these complications have been due to improper healing of the anastomosis between ureter and bowel. In a few cases bowel fistulas have developed at other sites and have presumably been due to bowel injury, impairment of blood supply or perhaps radiation change.

It would be well to point out some of the other factors present, which militate against a favorable anastomosis, before the type of ureterostomy performed is discussed.

Primarily, one is dealing with a damaged kidney as noted by the fact that over half the patients show evidence of major damage in the preoperative workup. Such a kidney can ill withstand the added insult of a shocking operation or the complications of a poorly functioning anastomosis.

After the pelvic evisceration an extensive, raw, unperitonealized area remains. The loss of electrolytes and protein-rich exudate from this raw area in the pelvis approaches 2 liters in the first twenty-four hours alone. The patient is in a state of negative nitrogen balance for two weeks after the operation.

The results on the urinary tract are twofold. In the first place the physiologic state is that of an extensive burn. All the complications incident to an extensive burn are thus thrown upon a kidney already damaged by disease and the shock of a prolonged operation. Secondly, the hypoproteinemia resulting from the fluid loss affects the normal healing of the anastomosis. Edema at the site of the anastomosis contributes to the urinary stasis, and poor function or breakdown at the site of the ureterointestinal junction may occur as circulation is impaired and infection appears. The resultant urinary block is then referred back to a kidney already damaged, and a vicious circle is present.

To these factors must be added the effect of the previous radiation on the lower ureters and bowel. Ninety-five per cent of the patients had had a complete course of radiation therapy. One is therefore dealing with tissue whose circulation may be regarded as abnormal. It might be possible to avoid this factor by discarding the pelvic ureter and using only the normal ureter above the pelvic brim.

Choice of Method in Diverting the Urinary Stream

Ureteroenterostomy

In the light of past experience, certain rules should be set up to govern the choice of ureteroenterostomy as the method of establishing urinary drainage. In general, it should not be chosen when there is evidence of an established pyelonephritis or when there is a low renal reserve secondary to an underlying nephritis. This may best be judged by the phenolsulfonephthalein test together, with an estimate of the size of the renal mass and thickness of the cortex as seen by x-ray study. This gives a better evaluation of the renal function than the apparent function noted on intravenous urography. If the renal function is only moderately impaired, or is due to back pressure alone without underlying nephritis, ureteroenterostomy may be perfectly safe even in the presence of considerable hydroureter and hydronephrosis. Under these circumstances the hydronephrosis and hydroureter gradually disappear, and the renal function remains excellent.

Cutaneous Ureterostomy

When one or both kidneys show evidence of damage or infection it is more logical to perform a bilateral ureterostomy, either as part of the complete operation or as a preliminary step in a staged operation, than to attempt to transplant the ureters into the bowel. Cutaneous ureterostomy is particularly useful when the patient has one nonfunctioning kidney, with the other badly damaged but uninfected. If the other kidney is infected it too should be brought to the skin rather than ligated. When the kidneys are not infected the patient gets along very well with one normally functioning kidney. The chief disadvantage in performing cutaneous ureterostomy is the recognized difficulty in providing a satisfactory ostium in a normal ureter. The thickened ureter of hydronephrosis provides a much more satisfactory opening. Despite its disadvantages, there is a real place for cutaneous ureterostomy in the management of these cases.

Technic of Anastomosis

The type of anastomosis employed in these cases has been the simple stab wound. The results have been unpredictable. Before one condemns the method it is well to remember the contributing factors already mentioned as well as to observe that the actual performance of the stab-wound anastomosis may have been faulty. Of necessity, this part of the operative procedure, which is most delicate and meticulous, is performed at the end of a long operation when neither the surgeon nor the patient is in best condition. For this reason it has been suggested, but as yet not tried, that the operation be

staged and urinary drainage be properly established at a preliminary operation before one attempts to complete the pelvic evisceration.

It may be well to consider some other type of anastomosis. More recent experience, which does not extend back far enough to evaluate the late results, suggests that the end-to-end mucosal anastomosis of Nesbit and Cordonnier combined, with the trough principle of Coffey, may have much to recommend it. This is done at the expense of increased operating time but provides a smoother convalescence. It is our opinion that no patient should be allowed to die on either early or late convalescence from obstructive urinary disease due to a poorly functioning ureteroenterostomy.

Summary and Conclusions

Although the operative mortality and postoperative morbidity from ultraradical surgery for cancer of the cervix has been high, the operation is probably sound in principle but requires perfection of many details. The fact that 9 of the 29 patients have lived from twelve to twenty-one months suggests that the procedure may be useful in certain cases of cancer of the cervix. What one may expect in the way of long-time survival is problematical. It is not inconceivable that a few patients may be cured.

Radical pelvic operations were performed on 29 patients with advanced carcinoma originating in the vagina, cervix and uterus.

The chief problem was the management of urinary-tract complications.

An analysis of the experience in disposition of the urinary drainage and treatment of urinary-tract complications is presented.

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PANCREATIC CARCINOMA WITH UNUSUAL METASTASIS TO THE SKIN AND SUBCUTANEOUS TISSUE SIMULATING CELLULITIS*

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IT IS the object of this report to call attention to an unusual metastasis of pancreatic carcinoma, simulating cellulitis, and to re-emphasize the importance of early, prompt biopsy.

Case Report

A 60-year old Navajo was referred to the Navajo Medical Center from the United States Indian Hospital, Shiprock, New Mexico, because of a hard cutaneous and subcutaneous swelling of the right side of the face and neck, and suprasternal area that was progressive and had begun with a small pimple of the right cheek 3 or 4 weeks previously. There had been progressive difficulty in swallowing as well as hoarseness. There had been no febrile reaction or leukocytosis; the patient had not responded to 4 days of therapy with penicillin and sulfadiazine.

Upon admission on September 19, 1949, physical examination showed a cellulitis, warm to the touch, extending from the right infraorbital area to the postauricular area, to the sternocleidal junction and posteriorly to the right of the trapezius muscle. This was a hard, indurated mass with bluish discoloration. The clinical impression was massive cellulitis of the right side of the face, neck and chest. Until October 19 the patient was treated with penicillin, sulfadiazine, aureomycin, Benadryl, typhoid vaccine, oxygen, whole blood, Chloromycetin, vitamin K, adrenocortical hormone and morphine, under the impression that an inflammatory reaction was the primary disease. It was believed on one occasion that the patient was suffering from an actinomycotic, spreading lesion. During the 30 days of therapy, he failed to show a leukocytosis or elevation of temperature, the exception being that a rise in temperature followed an emergency attempt at tracheotomy on October 15 and that a leukocytosis followed the therapeutic use of typhoid vaccine.

Figure 1 shows the discoloration of the skin and edema of the right side of the face and suggests the marked induration of the tissues of the right side of the neck and suprasternal region. At the time of attempted tracheotomy, it was observed that the tissues were of such stony-hard consistence that the attempt had to be abandoned. The incision seemed to relieve the tension somewhat, and the respirations were less labored.

A biopsy (Fig. 2 and 3) from the right cervical region 30 days after entry to the hospital showed skin and subcutaneous tissue with a sea of cells in the corium and deeper tissue characterized by large irregular, round cells with a large, round, hyperchromatic nucleus and numerous mitoses. Brown pigment was thought to be present in a few cells. The diagnosis was malignant melanoma, with the suggestion, however, that a search be made for a primary focus elsewhere. Sections taken from the biopsy were submitted to Hamilton Montgomery, of the Mayo Clinic, and to H. E. MacMahon, of Tufts College Medical School, Boston; the former offered the opinion that the section contained a highly malignant neoplasm (Grade 4) and the latter made a diagnosis of metastatic carcinoma to skin and subcutaneous tissues and suggested the stomach as a primary site.

All therapy was discontinued after these reports, and the patient was discharged to his home.

Examination of the blood on October 8 showed a red-cell count of 4,150,000, with a hemoglobin of 82 per cent, and a white-cell count of 15,000 (1 day after typhoid vaccine), with 17 per cent stab forms, 76 per cent segmented neutrophils, 6 per cent lymphocytes and 1 per cent monocytes. The fasting blood sugar was 140 mg. per 100 cc. The urine gave a ++ test for albumin and a negative test for sugar. On November 11 the nonprotein nitrogen was 55 mg., and the fasting blood sugar 110 mg. per 100 cc.

The patient died on November 15, about 2 weeks after discharge to the United States Indian Hospital at Shiprock, New Mexico.

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The opinions and views of this article are those of the author and do not necessarily reflect those of the United States Indian Service.
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Permission was granted for examination of the thorax and abdomen. Autopsy showed massive edema of the right side of the face and unusual induration of the skin and underlying tissues of the right side of the neck and the suprasternal area, extending beyond the midline to the left. There was a slightly gaping, midline, suprasternal incision (attempted tracheotomy) and another incision (site of biopsy) in the right posterior cervical region.

FIGURE 1. *Photograph Taken Two Weeks before Death, Showing Edema, Discoloration and Induration of the Skin.*

The subcutaneous tissues of the neck and suprasternal region contained a most unusually hard, yellow-gray tissue infiltrating and replacing all normal structures. The larynx and trachea were severely compressed by this massive growth. The lungs revealed severe bronchopneumonia and edema.

Examination of the abdomen demonstrated that the body and the tail of the pancreas contained fairly well defined, white-gray, very firm foci, which lay adjacent to and blended with the normal pancreas. There was no evidence of metastasis to the lymph nodes at the head of the pancreas. A solitary metastasis was seen in the mesentery of the small intestine.

Histologic study revealed that the pancreas was the seat of a carcinoma characterized by a sea of large, round cells containing a large hyperchromatic nucleus and showing many mitoses. The cells resembled in every detail the cells in the biopsy section from the neck. The final anatomic diagnoses were carcinoma of the body and tail of the pancreas, with massive metastasis to the right side of the neck and the suprasternal region, and with compression of the larynx and trachea, bronchopneumonia and metastatic carcinoma to the mesentery of the small intestine.

Dr. Montgomery, who was informed of the final outcome, replied as follows in a personal communication: "Cutaneous metastasis of a carcinoma of the pancreas is most uncommon in contrast to the not uncommon metastasis of neoplasms of the gastrointestinal tract, genitourinary tract and breast."

Discussion

It was recently stated[1] that one should become sensitized to the possibility of carcinoma of the pancreas.

Bariety and his colleagues[2] reported a case of pancreatic cancer with cutaneous metastases, confirmed histologically.

The clinical features of inflammatory metastatic carcinoma of the skin are closely allied to those of erysipelas.[3] The skin becomes red, hot, pitted and edematous, and there is an ill defined, often marked induration of the skin and subcutaneous tissue. There is no chill, fever or leukocytosis.

The common clinical impression is that cancer of the body and tail of the pancreas is rather rare. Ingelfinger[4] stated that "a series based upon material at autopsy, however, may reveal that lesions of the tail of the pancreas occur much oftener than one would suspect after analyzing surgical material."

FIGURE 2. *Biopsy from the Right Cervical Region, Showing Skin and Subcutaneous Tissue with Dense Sea of Cells.*

In a review of 34 autopsies of pancreatic carcinoma by Grauer,[5] the body and tail were involved in 3 cases, and the body alone in 2. The same author

mentioned the desmoplastic property of pancreatic carcinoma that was a striking feature, clinically, of the tumor of the neck as seen in the case reported above. There were 3 cases of metastasis to the supraclavicular lymph nodes in this series.

Duff,[6] writing on carcinoma of the body and tail of the pancreas, cited Ransom, who found that the disease was characterized most constantly by severe upper abdominal pain frequently occurring in paroxysms, rapid and extreme emaciation and complete absence of jaundice. In 11 of the 16 cases of Ransom's series, carcinoma of the pancreas was unsuspected prior to operation or autopsy. Duff[6] analyzed a series of 16 cases of carcinoma of the body and tail of the pancreas from the records of the Johns Hopkins Hospital and pointed out that the most common initial symptoms were, in order of frequency, abdominal pain (14 cases), obstinate constipation (6 cases), belching of gas or eructations after meals (6 cases), swelling of the abdomen (5 cases) and weakness (5 cases). He also stated that 1 patient in his series showed metastasis from a pancreatic carcinoma to the left supraclavicular lymph nodes.

In the case reported above, the features of the clinical course that deserve emphasis are the induration, edema and skin discoloration, which impressed all examiners as cellulitis and which formed the basis of antibiotic therapy for about four weeks; the absence of any signs or symptoms pointing to a malignant process of the pancreas; and the absence of fever and leukocytosis, which are usual accompaniments of cellulitis. A further observation is the rapidity of the process in the neck and suprasternal area, which focused attention on the possibility of a spreading, inflammatory process.

The features from the pathological findings that deserve emphasis are that biopsy as a method of diagnosis should be performed oftener and earlier; in a patient who is clearly not responding to therapy and lacks the classic signs of fever and leukocytosis in the face of a clinical impression of inflammation, a primary carcinoma of the pancreas should be considered.

The primary pancreatic lesion showed only a solitary metastasis to the mesentery of the small intestine, and a most massive, rapidly growing spread to the cervical region, suprasternal area and tissues surrounding the larynx. As mentioned above, this tumor showed an unusual tendency to stimulate a desmoplastic response in the neck tissues.

Summary

A case in which the patient was treated for cellulitis and was found, after biopsy, to be suffering from a malignant tumor is reported.

The patient showed signs that were believed to be consistent with an inflammatory process: edema, color change of the skin, warmth of the skin and induration. There was no elevation of temperature or leukocytosis. After biopsy and the establishing of a diagnosis, death occurred, and autopsy revealed a primary carcinoma of the body and tail of the pancreas, which had metastasized massively to the neck and suprasternal region.

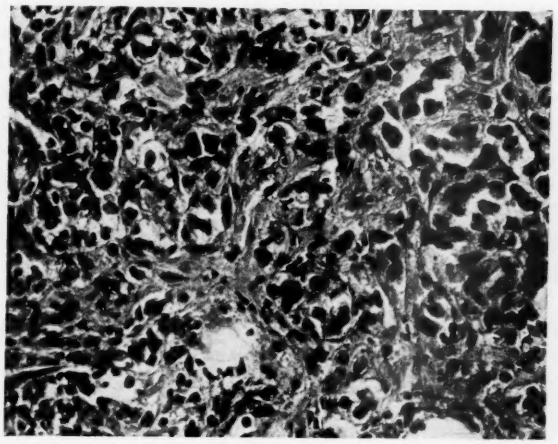

FIGURE 3. *Biopsy from the Right Cervical Region, Showing Higher Magnification of a Field from Figure 2, and Containing Malignant Epithelial Cells.*

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FAILURE OF CHLORAMPHENICOL IN A CHRONIC TYPHOID CARRIER*

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THE recent introduction of the new antibiotic, chloramphenicol (Chloromycetin), has led to clinical trials in acute typhoid fever and in the chronic carrier state. Woodward and his associates[1] reported a beneficial effect in acute typhoid fever. The initial oral dose was 50 mg. per kilogram of body weight, followed by a maintenance dose of 0.25 gm. every three or four hours, this dosage level being gradually reduced as the temperature fell by lysis. Similarly encouraging results have been recorded and appear impressive.[2-4] A survey of the literature reveals that the several case reports dealing with the treatment of the chronic carrier state give uniformly disheartening results.[4, 5] The purpose of this communication is to record an attempt to treat a chronic typhoid carrier with larger doses of Chloromycetin than have heretofore been tried.

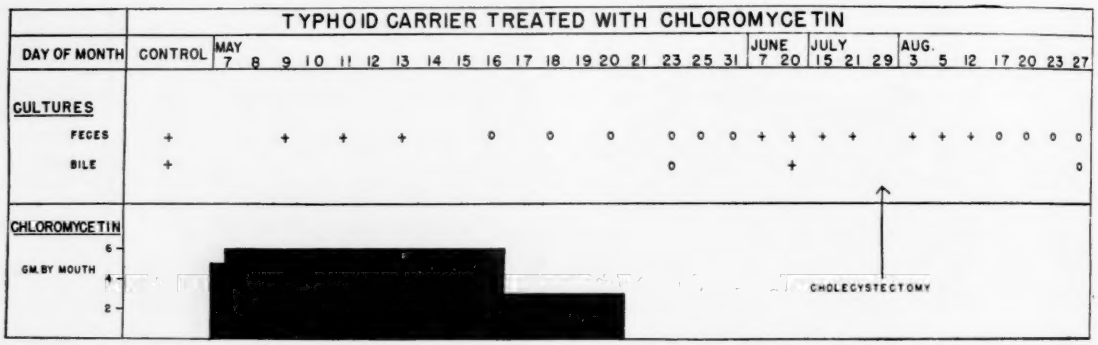

FIGURE 1. *Effect of Chloromycetin on Cultures for* S. Typhi *Organisms in the Stool and Bile. Two stool cultures obtained on follow-up examination four and a half months after cholecystectomy were positive for* S. typhi.

CASE REPORT

A 70-year-old unemployed man was admitted to the hospital on March 31, 1949, complaining of "stomach trouble." For the last 10 to 12 years he had noted episodes of postprandial "gas," abdominal distention, nausea without vomiting, vague abdominal cramps and intolerance to fatty and greasy foods. Except for rare attacks of diarrhea, there had been no other gastrointestinal symptoms. His weight had been constant. Approximately 44 years prior to admission, 7 to 10 days after cleaning out a privy, he had a prolonged febrile illness, with abdominal cramps, slight diarrhea, and mental confusion. He recalled being told that this illness was typhoid fever. The patient was unaware of the carrier state and had never been a food handler. While serving in the Army in World War I, he had received "some typhoid shots." The remainder of the past history was irrelevant.

Physical examination revealed a well developed, well nourished man with normal temperature, pulse and respiratory rate. The body weight was 153 pounds (70 kg.). The blood pressure was 120/70, the lungs were clear, and the heart was normal. Examination of the abdomen showed a well healed right-lower-quadrant appendectomy scar; no spasm, tenderness, organs or masses were noted. The remainder of the physical examination was negative.

A complete blood count, blood Kahn test, erythrocytic sedimentation rate, barium enema, chest x-ray examination, electrocardiogram and upper gastrointestinal series were within normal limits. A gall-bladder study with oral administration of Priodax showed a nonfunctioning gall bladder without evidence of radiopaque calculi.

The temperature was normal throughout the hospital course. During the 2nd hospital week, semisolid, nonbloody diarrhea developed. Stool culture revealed moderate numbers of gram-negative bacilli, which were morphologically, serologically and culturally identical with *Salmonella typhi*. The organism was not phage-typed. It was found resistant to penicillin and sensitive to streptomycin, aureomycin and Chloromycetin. A urine culture was negative for the organism. Agglutination tests of the patient's serum with *S. typhi* antigen revealed an "H" titer of 1:40 and an "O" titer of 1:20. Duodenal drainage was done under fluoroscopic control. Cultures of the bile were positive for *S. typhi*. Each stool specimen obtained before the beginning of therapy was positive for the organism.

The patient was given a 14-day course of Chloromycetin therapy. The initial oral dose was 5.0 gm. (70 mg. per kilogram of body weight), followed by 0.5 gm. every 2 hours for 10 days (80 mg. per kilogram of body weight), and 0.5 gm. every four hours for 4 days (40 mg. per kg.). The total dose of Chloromycetin was 80 gm. Figure 1 shows the bacteriologic findings during and after this treatment. Throughout the period of therapy, serial serum nonprotein nitrogen values, urinalyses and blood counts revealed no deviation from normal, and no fever or skin rash was noted. The only untoward effect was moderately severe nausea without vomiting at the end of the 1st week. This symptom compelled a reduction in the daily dosage, with slight diminution in nausea. Stool cultures obtained at regular intervals showed 3 positive cultures during the first 7 days of therapy. Three stool cultures taken during the 2nd week of treatment were negative. Culture of the bile obtained by duodenal drainage 2 days after cessation of therapy was negative for *S. typhi*. However, 17 days after completion of the therapeutic trial, the stool and bile cultures again became positive for this organism. At cholecystectomy 60 days after discontinuance of therapy, the gall bladder presented the typical appearance of chronic

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cholecystitis. The remainder of the extrahepatic biliary tree was normal. Immediately after removal of the gall bladder, culture of its bile was positive for *S. typhi.* Culture of the interior of the large solitary calculus was likewise positive for this organism. Microscopical study of the gall bladder confirmed the gross impression of chronic cholecystitis. Stool cultures were positive until the 14th postoperative day. All stool specimens and 1 bile culture were then negative during the patient's last month in the hospital. However, at follow-up examination 3 months after discharge, all stools were positive for *S. typhi.*

Discussion

Although this case presented encouraging bacteriologic results during the trial of Chloromycetin therapy, the return of positive stool and bile cultures following cessation of the course confirms the discouraging final results of other investigators.[4, 5] The well documented beneficial results in acute typhoid fever stand in contrast to those in the chronic carrier state. The reasons for such a failure in this patient are not clear, but the tenacity of his carrier state is attested to by its continuance after the surgical removal of an obvious focus of typhoid bacilli. The bacteriologic course in this case again demonstrates the need for long-term follow-up study in such patients, to take into account the natural intermittency of the excretion of typhoid bacilli.

Summary

An unsuccessful attempt to cure a case of the chronic typhoid-carrier state of the gall-bladder type, employing chloramphenicol (Chloromycetin) in a total dosage of 80 gm. in fourteen days, is presented.

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MEDICAL PROGRESS

THE CLINICAL USEFULNESS OF ACTH AND CORTISONE*

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BOSTON

OVER the past two decades reports on the beneficial effects of adrenocortical extracts in such varied disorders as pemphigus,[1] vomiting of pregnancy[2] and disturbances of neuromuscular function have appeared.[3] Improvement, although often encouraging, was usually transient and difficult to reproduce. The high cost of adrenal extracts and their relatively low potency made it impractical to use pharmacologically effective doses of hormone for prolonged periods. Furthermore, in patients with normal adrenal glands there was the added difficulty of compensating for the suppression of pituitary adrenocorticotrophic hormone (ACTH) production that accompanies the administration of biologically active adrenocortical steroids. These difficulties are best illustrated by the fact that it was not until eight years after potent extracts became available clinically that an unequivocal, although transitory, metabolic effect of adrenal steroids was demonstrated in normal human subjects.[4] The synthesis of Cortisone,[5] the isolation of ACTH[6, 7] and their subsequent large-scale production have made it possible for the first time to maintain elevated levels of adrenal steroids even in patients with normal adrenal glands.

Pituitary adrenocorticotrophin (ACTH) and Cortisone (Compound E) have now been available to clinical investigators in increasing quantities for approximately three years. During this relatively short period marked progress has been made toward an understanding of their clinical potentialities.

Prior to the remarkable discovery of Hench and his associates on the use of Cortisone and ACTH in the treatment of rheumatoid arthritis[8] and of Cortisone in rheumatic fever,[9] the clinical use of the small quantities of ACTH available was limited

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to studies of its metabolic effects by Browne[10] and others[11-13] and the direct clinical applications that these effects suggested: in a diagnostic test for Addison's disease and for the measurement of adrenocortical reserve[14]; in the treatment of adrenal insufficiency secondary to anterior pituitary failure[15]; as an adjunct in the treatment of idiopathic hypoglycemia[15]; for the relief of gouty arthritis[16, 17]; and for their effect on lymphatic leukemia and diseases associated with eosinophilia.[18] Cortisone had been

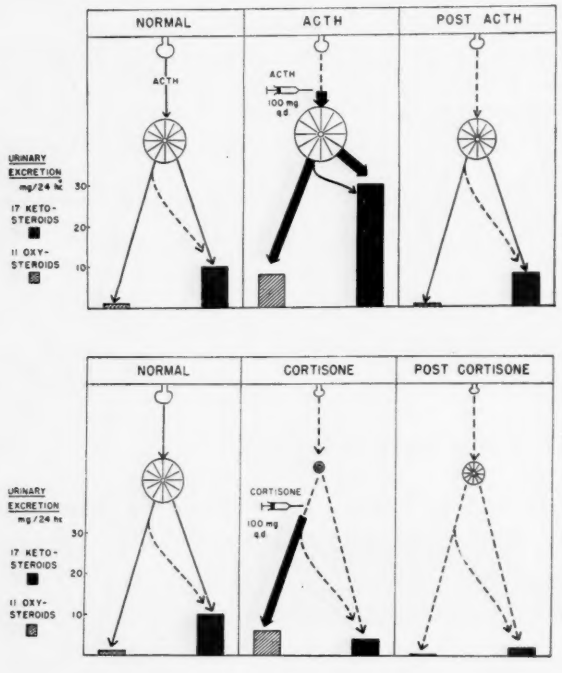

FIGURE 1. *Effect of ACTH and Cortisone on Pituitary and Adrenal Activity; These Schematic Diagrams Depict the Release of 11,17-Oxysteroids (the Term "11,17-Oxysteroids" Is Used throughout to Denote the Neutral Reducing Steroid Fraction of the Adrenal Cortex Related to Cortisone and Compound F) and 17-Ketosteroids by the Adrenal Gland as a Consequence of ACTH Stimulation by the Anterior Pituitary Body and the Secretory Readjustments that Follow the Administration of Exogenous ACTH or Cortisone.*

Either preparation induces anterior pituitary hypofunction, owing to increased endogenous production of adrenal steroids after ACTH administration and to the administered steroid itself after Cortisone. At the end of administration of ACTH the delayed return of the hypoactive pituitary function to normal temporarily deprives the hypertrophied adrenal cortex of stimulation and leads to transient adrenal hypofunction as measured by steroid excretion. After Cortisone the marked cortical atrophy accentuates temporary adrenal hypofunction.

used only in the treatment of Addison's disease[19-21] and Addison's disease complicated by diabetes mellitus[22, 23] and in a preliminary study of its effect on hypertension in man.[21]

Hormone Preparations

ACTH

The majority of clinical studies, including our own, have been carried out with ACTH prepared by the Armour Laboratories,* a pituitary adrenocorticotrophin derived from pork pituitary glands by an isoelectric precipitation method. It is available commercially as a sterile powder that may be dissolved in isotonic saline solution for intramuscular administration. This preparation contains minute, and physiologically insignificant, quantities of other pituitary hormones as well as inert protein. Other ACTH preparations that have been used in man are those derived from the pituitary glands of sheep,[6] a polypeptide mixture prepared from the pituitary glands of sheep by Li[24] and a glacial acetic acid extract from pork pituitary glands prepared by Astwood.[25] In the near future, beef ACTH preparations may also become available commercially in this country.

Preparations of ACTH are usually assayed and expressed in terms of milligrams of the Armour Standard La-1-A.[12] The majority of these preparations contain a protein molecule of 23,000 molecular weight. A heat-stable polypeptide mixture has been prepared[24] and shown to be as potent as the large molecule.[26]

Experience has demonstrated that the minimal effective dose of ACTH in man consists of 5 to 20 mg. administered every six hours intramuscularly. A single dose will show a measurable effect within thirty minutes; the changes will be maximal in four hours and no longer noticeable after eight to twelve hours. It has been advocated by some that the dosage be gradually reduced while the interval of administration is kept constant in ending a course of therapy, to prevent a sudden collapse of adrenocortical function. Toxicity is minimal since a single dose of as much as 200 mg. given intravenously to an experimental subject produced no marked untoward effects.[13]

Cortisone

Cortisone (17-hydroxy-11-dehydrocorticosterone), or Compound E of Kendall, is prepared by partial synthesis from bile acids.[5] Cortisone acetate (Cortone, Merck) is available as a microcrystalline suspension of the acetate in saline solution. An identical preparation, Cortisone (Ciba) has become available. The slow absorption of microcrystalline suspensions of Cortisone in saline solution accounts for a duration of action extending over a twenty-four-hour period and a definite cumulative effect that lasts at least three days after prolonged therapy. Cortisone is excreted in the urine in quantities not exceeding 5 per cent of administered material, and a fraction appears to be converted to 17-ketosteroids and excreted as such in the urine (Fig. 1). We have prepared and used Cortisone acetate pellets[20] in the treatment of Addison's disease.

Comparison of Effects of ACTH and Cortisone

ACTH produces its therapeutic effects by stimulating the adrenal cortex to increase the secretion

*We are indebted to Dr. John R. Mote, of the Armour Laboratories, for providing the ACTH used in these studies

of adrenal steroids,[12] including Cortisone and closely related compounds.[11] The effectiveness of ACTH and Cortisone appears to vary directly with the level of circulating adrenocortical hormones obtained and with the responsiveness of the tissues on which they act. A limiting factor in the response to ACTH is the capacity of the adrenal cortex to react to stimulation. Before final evaluation of the clinical usefulness of ACTH is made, the degree of adrenocortical activation should be measured. Unless adrenocortical activation can be demonstrated by such technics as the fall in circulating eosinophils or the rise in urinary excretion of 17-ketosteroids or 11,17-oxysteroids, no conclusion should be drawn regarding its therapeutic efficacy. It should be noted that a significant fall in circulating eosinophils may occur on occasion after ACTH administration with only a minimal increase in urinary 17-ketosteroid excretion and without any significant clinical response. In such cases it is apparent that the eosinophil response is too sensitive an index of adrenocortical activation. Conversely, in patients with certain allergic eosinophilias clinical response has been noted without a significant fall in circulating eosinophils, but accompanied by a rise in urinary 17-ketosteroid excretion. It is apparent that a fall in circulating eosinophils, although usually highly sensitive, is not always as reliable a measure of the degree of adrenocortical activation as the increase in the daily 17-ketosteroid and 11,17-oxysteroid excretion. In general, Cortisone in daily doses of 50 to 200 mg. produces a much less striking fall in circulating eosinophils than ACTH in doses of 40 to 100 mg. daily, although the clinical response may be identical. This supports the observation that eosinopenic compounds more potent than Cortisone, such as 17-hydroxycorticosterone (Compound F), are secreted by the adrenal cortex.[27]

It appears that a given quantity of ACTH may elicit a variable increase in adrenal steroid output, depending upon the state of activity of the adrenal cortex at the time therapy is instituted. Thus, a quiescent gland may respond minimally to a standard dose of ACTH, whereas a very active gland may show a tremendous absolute increase in hormone output. It is possible, however, to stimulate a relatively inactive gland to high levels of activity by prolonged therapy. It is conceivable that continuous excessive stimulation of the adrenal glands may lead to exhaustion; however, this rarely occurs with the dosage and duration of therapy employed at present. Refractoriness to the ACTH preparations of a particular species may develop. This rarely occurs with a single prolonged period of hormone administration, but is found on occasion with repeated courses of treatment. Refractoriness may be detected and overcome by the substitution of an equivalent dose of ACTH derived from another animal source.

In evaluating the therapeutic effects to be expected from Cortisone therapy, one must bear in mind that, whereas Cortisone administration adds directly to the level of adrenal steroids in body fluids, it also suppresses the secretion of endogenous steroids by inhibiting pituitary ACTH production. For this reason, the more active the adrenal gland, the less effective will be a given quantity of Cortisone. Thus, 50 to 100 mg. of Cortisone administered to a patient with a very active adrenal cortex will actually result in an over-all decrease in circulating adrenal hormone.

After the withdrawal of prolonged Cortisone therapy there is a period of adrenal atrophy (four to ten days) during which the adrenal cortex responds minimally or not at all. After a prolonged period of ACTH therapy, there ensues a period of adrenocortical inactivity within the third, fourth and fifth days after discontinuation of therapy as a result of temporary pituitary ACTH suppression. The period of relative adrenocortical insufficiency is much more pronounced and more prolonged after Cortisone than after ACTH therapy.

ACTH, by stimulating the secretion of a great variety of adrenal steroids, may produce effects other than those obtained with Cortisone treatment alone. Whether ACTH therapy has distinct advantages or disadvantages over Cortisone as a consequence of this is not known at present.

Mechanisms of Action of ACTH and Cortisone

In an attempt to understand the manner in which Cortisone and ACTH modify pathologic processes, it may prove helpful to review briefly some of the more important effects that Cortisone and related adrenal steroids are known to exert on physiologic mechanisms. To simplify discussion, these effects will be considered under six general headings: effects on other endocrine systems; specific metabolic effects of 11,17-oxysteroids; neuromuscular effects; immunologic effects; cytologic effects; and effect on specific enzyme systems.

Effects on Other Endocrine Systems

ACTH and Cortisone exert a definite influence on the function of the thyroid and posterior pituitary glands, and on insulin secretion. Thus, in interpretations of the over-all actions of ACTH and Cortisone and the possible mechanisms by which clinical improvement is obtained, the specific effects of the adrenal hormones on these other endocrine organs must be considered.

Adrenal cortex and thyroid gland. Long-continued ACTH or Cortisone treatment may depress thyroid function as measured by the uptake of radioactive iodine by the gland, the level of serum protein-bound iodine and the basal metabolic rate.[20, 28, 29] It is possible that the depression of thyroid activity occurs as a consequence of the partial inhibition of the thyroid-stimulating hormone similar to the

partial pituitary inhibition that appears to take place — for example, with high levels of estrogens.[30] On the other hand, a high level of circulating adrenal steroid may augment the peripheral effectiveness of thyroid hormone. Such an action, ordinarily masked by the inhibitory effect noted above, has been demonstrated experimentally in athyreotic patients maintained on a constant dose of thyroid medication, in whom Cortisone induces a rise in the basal metabolic rate.[29]

Adrenal cortex and posterior pituitary body. It is known that patients with Addison's disease exhibit abnormally high levels of antidiuretic activity in their blood and urine. One manifestation of this alteration in hormone balance is the retention of water observed in patients with Addison's disease after the standard water test (Robinson–Kepler–Power). Desoxycorticosterone does not correct this disorder, whereas Cortisone in adequate doses may restore the response to normal.[31] Whether the effectiveness of Cortisone in reducing the excess antidiuretic activity in Addison's disease is due to depression of posterior pituitary activity or to a utilization or destruction of the antidiuretic material is not known.[32]

Adrenal cortex and pancreatic islet cells. Insulin antagonizes the tendency of ACTH and Cortisone to reduce the utilization of carbohydrate and to stimulate gluconeogenesis. The impairment in utilization of carbohydrate with increased production results in hyperglycemia and an increased demand for insulin. In most patients this is adequately met by increased insulin production. In rare cases diabetes develops in patients unable to meet the excessive demand for insulin secretion. After the withdrawal of ACTH or Cortisone, the patient may experience a period of relative hypoglycemia as a consequence of persistent insulin overproduction.[19, 33, 34]

Adrenal cortex and gonadal function. The high level of circulating adrenal steroids induced by ACTH or Cortisone treatment tends to depress gonadal function, possibly through partial inhibition of pituitary gonadotropin secretion. Inhibition of follicle-stimulating-hormone production has been suggested by the complete, but temporary disappearance of menopausal hot flashes during ACTH administration in 1 patient. This was not found by others to occur with Cortisone.[35] In women, menstruation is frequently delayed or inhibited during Cortisone or ACTH administration.

Specific Metabolic Effects of 11,17-Oxysteroids

Electrolyte regulation. Cortisone induces a slight initial urinary sodium and chloride retention with transiently increased potassium excretion.[20] With continued administration of the hormone, increased sodium and chloride *excretion* may occur; potassium may be retained in conjunction with increased glycogen deposition in quantities sufficient to offset partly the increased excretion of this ion that would normally be expected with increased protein breakdown.

With ACTH administration water, sodium and chloride *retention* is usually more marked than with even large quantities of Cortisone. This may occur because greater quantities of Cortisone-like or desoxycorticosterone-like steroids are secreted by the adrenal glands in response to ACTH or because of the antidiuretic contaminant of ACTH. Both Cortisone and ACTH given in large doses over a prolonged period will induce a hypokaliemic, hypochloremic alkalosis similar to that observed in Cushing's syndrome and presumably based on a change in ionic distribution within the various fluid compartments.[35, 36] Increased calcium and phosphorus excretion may occur with either Cortisone or ACTH therapy.[12, 35]

Carbohydrate, fat and protein metabolism. ACTH and Cortisone increase glycogen deposition in the liver, partly by increasing gluconeogenesis from amino acids and at the same time opposing the action of insulin peripherally. Impaired or restricted carbohydrate utilization is accompanied, as might be anticipated, by increased mobilization and utilization of fat, thus further conserving carbohydrate stores and permitting the patient to withstand the effect of starvation or carbohydrate deprivation more effectively.[20]

Cortisone, as well as ACTH, tends to increase urinary nitrogen excretion and thereby produces a negative nitrogen balance. This is related to its antianabolic effect. A more striking result is the marked increase in the urinary excretion of uric acid, which falls off gradually with continued administration of these hormones. This effect is related, for the most part, to a change in the renal clearance of uric acid.

The effect of ACTH on nitrogen metabolism may differ quantitatively from that of Cortisone if adrenal androgens with a nitrogen-sparing effect are secreted in response to stimulation of the adrenal gland. The androgenic effects of ACTH are characterized by the development of hirsutism and acne during therapy.

Neuromuscular Effects

Changes in brain metabolism. The profound changes in neuromuscular function that accompany adrenocortical insufficiency (Addison's disease) on the one hand and adrenocortical hypersecretion (Cushing's syndrome) on the other are well known. Of particular interest, however, are the characteristic slowing of the alpha rhythm and the decreased number of beta waves observed in the electroencephalogram of a high proportion of patients with Addison's disease.[37] The cause of this disturbance is not definitely established, but it is known that restoration to normal requires the administration of relatively large quantities of 11,17-oxysteroids.

This type of adrenal steroid appears highly specific since desoxycorticosterone is not effective in this respect. One frequently observes increased irritability and alterations in personality accompanied by increased mental acuity and restlessness in Cushing's syndrome. These observations are helpful in appreciating the psychologic changes that may follow ACTH and Cortisone administration.

Anesthetic effect of steroids. An interesting property of the steroid hormones is their anesthetic action. Selye[38] has studied this property in great detail and believes it to be characteristic of a large group of steroids. Although Cortisone itself does not share this property, an analgesic effect may play a part in its therapeutic efficacy.

Changes in the function of the neuromuscular unit. An excess of Cortisone, producing hypokaliemia and hypochloremia, may lead to muscular weakness and paralysis. These changes in all probability originate from alterations in the distribution of potassium and chloride between cells and extracellular fluid. They are enhanced by concomitant sodium retention, which results in a greatly decreased ratio of potassium to sodium. After the withdrawal of Cortisone following prolonged therapy, potassium may be retained in excess and sodium lost in the urine as a consequence of the adrenocortical atrophy that may persist for seven to ten days.[35, 39] Under these circumstances, impaired neuromuscular function may again develop, this time as a consequence of an abnormally high potassium-sodium ratio.

Changes in muscle metabolism. Muscular dysfunction characteristically manifests itself by increased creatinuria and a negative nitrogen balance. The adrenocortical steroids of the 11,17-oxy type tend to reduce the rate of carbohydrate utilization by muscle cells and to induce a negative nitrogen balance accompanied by a loss of creatine. Except so far as these hormones affect particular metabolic pathways within the muscle cell, it appears that the over-all effect of excessive 11,17-oxysteroid secretion would not be beneficial in maintaining optimal neuromuscular function.

Immunologic Effects

Antibody production. Interest in the possible immunologic effects of adrenal steroids was stimulated by the observations of Dougherty, White and Chase, who have marshaled an impressive array of evidence from animal studies to support the hypothesis that certain adrenal steroids lead to an increase in circulating antibodies and that this effect is brought about through involution of lymphoid tissue and a release of antibodies contained within the cells.[40] Recent in vitro evidence supports these findings.[41] However, the results of Eisen et al.,[42] using an accurate chemical technic for estimating the circulating antibodies, failed to support some of these observations. In man, Mason et al.[11] and Forsham et al. [12] found no rise in gamma globulin after repeated administration of ACTH. Patients with disseminated lupus treated with ACTH have shown a fall in the high serum level of gamma globulin at the time of clinical improvement. Finally, Herbert and deVries[43] found that large doses of ACTH given to human subjects in acute experiments produced no demonstrable effect on the level of circulating antibodies, although the typical diminution in the number of circulating lymphocytes occurred.[43] Present evidence thus fails to support a significant effect of adrenal steroids on antibody formation in man.

Reaction to antigen. Inhibition of the local reaction to intradermal injection of tuberculin in hyperimmune guinea pigs has been demonstrated after ACTH and Cortisone administration.[44, 45] It has also been shown that the in vitro cytolysis by tuberculin of lymphocytes from an immunized animal is inhibited if the animal is given ACTH for at least a week prior to the test.[44] ACTH has been found to inhibit the development of arteritis and cardiac lesions following the injection of horse serum into sensitized rabbits,[46, 47] and both ACTH and Cortisone prevented anaphylactoid reaction of rats to parenteral egg-white administration.[48] Anaphylaxis in the guinea pig was not prevented by ACTH,[49] and cytotoxic serum nephritis in rats occurred in spite of pretreatment with Cortisone.[50] Although reports of the capacity of ACTH and Cortisone to alter positive skin tests to a variety of bacterial antigens in man have been somewhat contradictory,[51-53] it is becoming clear that adrenal hormones are capable of inhibiting at least delayed ("tuberculin-type") reactions when administered in adequate doses for a sufficient period.[52]

Anaphylaxis and histamine metabolism. It has long been known that adrenalectomized animals are more vulnerable to anaphylactic reactions than normal controls[54] and that such animals are also more sensitive to histamine.[55] It has been established that adrenalectomy leads to a rise in histamine content[56] and a fall in histaminase content[57, 58] of rat tissues, and that these phenomena can be reversed by adequate doses of adrenocortical extract. Asthmatic patients treated with ACTH have been observed to excrete decreased quantities of histamine and increased quantities of histidine in the urine. These chemical changes have paralleled clinical improvement.[53] Although an increased level of adrenal steroids may increase the breakdown of histamine and reduce its rate of formation, they do not prevent the local or general reactions to histamine injected as such.[51, 52]

It thus appears possible that the adrenal steroids alter the allergic tissue reaction that follows the union of antigen and antibody. One proved mechanism involved in this reaction is the demonstrated ability of these hormones to inhibit the formation of histamine and accelerate its break-

down. *It appears that the action of ACTH and Cortisone may dissociate the harmful effects of hypersensitivity from the beneficial reaction of immunity.*

Cytologic Effects

Erythrocytic series. Either Cortisone or ACTH has been shown to induce a transitory reticulocytosis in man in a variety of diseases including rheumatoid arthritis,[59] Still's disease,[59] disseminated lupus and pernicious anemia. ACTH appears to counteract effectively the unknown cause of anemia associated with some of these disorders. In diseases characterized by bone-marrow invasion, such as acute lymphatic leukemia and multiple myeloma, reticulocytosis may also follow ACTH therapy.[60] In this instance a decrease in the cellularity of the invading tumor in the bone marrow is postulated as an additional mechanism of improving erythropoiesis. Aplastic anemia is refractory to ACTH.[60]

Polycythemia has been a well recognized accompaniment of Cushing's syndrome,[61] and it seems possible that 11,17-oxysteroids or Cortisone-like hormones are responsible for this change. The sustained increase in erythrocyte counts observed in patients treated for periods of two weeks or more with ACTH[59] or Cortisone[35] supports this assumption.

Leukocytic series. Animal experiments have demonstrated clearly that both ACTH and Cortisone produce a striking neutrophilia. This finding has been confirmed in man.[12, 20] The effect on neutrophils is more marked in children, in whom a marked neutrophilia may persist throughout the period of hormone administration.

Dougherty and White[62] demonstrated the lytic action of Cortisone and ACTH on fixed lymphoid tissue and circulating lymphocytes. Heilman[63] showed a specific necrotizing effect of Cortisone on lymphocytes in tissue culture that was not shared by desoxycorticosterone (DOCA). Heilman and Kendall[64] were able to demonstrate a marked arrest of the growth of a malignant lymphoid tumor in the mouse by the administration of Cortisone. In man the lymphopenic action of ACTH and Cortisone was demonstrated by Hills et al.[18] and Thorn and his co-workers.[20]

Dalton and Selye[65] pointed out that a marked eosinopenia accompanied the alarm reaction, and Thorn and his associates[14] first demonstrated this effect in man after the administration of 25 mg. of ACTH. The circulating eosinophils are reduced after the administration of 11,17-oxysteroids or ACTH, but are not affected by desoxycorticosterone or 11,17-oxysteroids in physiologic quantities. In vitro studies have thus far failed to reveal a direct "lysing" effect of Cortisone or Compound F on eosinophils. Preliminary observations suggest that the most likely explanation for the eosinopenia induced by Cortisone or ACTH is the increased tendency for agglutination observed and the consequent destruction by the reticuloendothelial system.

In the presence of an eosinophilia the specific eosinopenic action of Cortisone and ACTH may be partly overshadowed by the increased production of these cells, whereas in conditions associated with bone-marrow hypoplasia, such as hypothyroidism and neoplastic invasion, the effect of a standard dose of ACTH and Cortisone on the initially low level of circulating eosinophils may be more marked, in terms of their percentile fall.

After the discontinuance of hormone therapy there is a rise in eosinophils within three days, characterized by a rebound over and above the initial pretreatment control level.

Platelets. To date, no effect of ACTH on platelets has been observed.

Macrophages. An increased phagocytosis has been noted during stress[66] and after the administration of ACTH.[67] A decreased phagocytic activity of the spleen has been reported to follow adrenalectomy.[68] The addition of Cortisone to cultures of spleen or lymph nodes increased the growth of macrophages and inhibited that of fibroblasts and lymphocytes.[63]

Fibroblasts. Retardation of wound healing in patients with Cushing's syndrome is well recognized. Ragan et al.[69] have demonstrated a decreased fibroblastic proliferation in wounds inflicted upon Cortisone-treated animals. Recently, it has been reported that certain patients treated with large doses of ACTH over a prolonged period may also encounter difficulty in the healing of wounds.[70] It has been assumed that this was the result of the antianabolic action of 11,17-oxysteroids. In our experience there has been no difficulty in wound healing of patients attributable to ACTH or Cortisone in *therapeutic* doses.

Effects on Specific Enzyme Systems

Gastrointestinal enzymes. Recent studies[71, 72] indicate that the administration of ACTH to normal subjects induces an immediate and marked increase in the gastric secretion of pepsin and in the urinary excretion of uropepsin, whereas gastric acidity remains unchanged. Functional gastric mucosa is necessary for the response. That the 11,17-oxysteroids are responsible for this effect is indicated by the increased urinary uropepsin excretion observed in patients with Addison's disease treated with Cortisone, whereas desoxycorticosterone is ineffective in this respect. Preliminary observations suggest that adrenocortical hormones also increase the gastric secretion of the soluble mucous fractions, mucoprotein and mucoproteose. A decrease in the elevated lysozyme activity in the feces of patients with ulcerative colitis has been reported after ACTH administration.[72, 73]

Hyaluronidase. Opsahl[74] observed that the intracutaneous spread of India ink was increased in mice after adrenalectomy and that the addition of hyaluronidase greatly augmented this effect. Furthermore, an inhibitory effect by corticosteroids upon the activity of hyaluronidase has been demonstrated.[75, 76] Seifter and his co-workers[77] have shown an antihyaluronidase effect of Cortisone after the injection of phenolsulfonphthalein, dye and hyaluronidase into joints of rabbits.[77] The increase in adrenocortical steroids induced by either epinephrine[78] or ACTH[79] appears to decrease the activity of injected hyaluronidase in the skin of human subjects. Hyaluronidase was found to be less active in patients with Cushing's disease than in normal subjects. Patients with Addison's disease treated with Cortisone tended to show a decreased response to hyaluronidase as compared with those maintained on desoxycorticosterone acetate alone.[79]

The mechanism by which 11,17-oxysteroids inhibit hyaluronidase is not known. Inactivation of the enzyme by Cortisone does not occur in vitro.[80]

Sulfhydryl systems. The metabolic activity of many cellular enzyme systems is known to depend upon the presence of active sulfhydryl (SH) groups. Recent evidence suggests that an excess of adrenocortical hormones plays a role in the metabolic inactivation of the SH groups. A reduction in blood glutathione level and a concomitant development of hyperglycemia and glycosuria have been reported by Conn et al.[81] after the administration of ACTH. It is also known that the diabetes of Cushing's syndrome is associated with a low blood glutathione level. The prevention of hyperglycemia and glycosuria occurring secondarily to excessive adrenocortical hormones by the administration of glutathione further supports this relation.[81]

Sulfhydryl compounds are also known to inhibit the oxidation of melanin precursors. Both ACTH[35] and Cortisone[20] have been noted to increase pigmentation of the skin and nails (Fig. 2). Whereas the possible melanophore content of ACTH preparations may explain the development of this pigmentation following ACTH, it fails to account for the development of pigmentation following crystalline Cortisone. It is suggested that increase in pigmentation observed with ACTH and Cortisone therapy may occur in part as a result of the inactivation of sulfhydryl groups in the skin, thus allowing for melanin deposition.[82]

Arginase. A significant increase in both liver and kidney arginase of mice has been noted to follow the subcutaneous implantation of pellets of Cortisone.[83]

Peptidase. After the injection of massive amounts of ACTH in man, an increase in serum peptidase activity has been demonstrated.[13]

Undesirable Aspects of ACTH and Cortisone Treatment

On the basis of evidence suggesting that 11,17-oxysteroids interfere with allergic reactions, true sensitivity due to any antigenic effect of ACTH derived from animal sources would scarcely be expected to constitute a serious problem in the use of ACTH or Cortisone. It is not surprising, then, that the signs and symptoms ordinarily associated with drug sensitivity, such as fever, dermatitis and arthritis, are noted very infrequently. Local tenderness and induration at the sites of intramuscular injections, although not uncommon, need not interrupt therapy with either drug.

It might also be anticipated that ACTH, prepared as it is from animal pituitary glands, might contain minute quantities of other anterior and posterior

Figure 2. *Pigmented Bands in the Nails of a Negro Treated for Three Weeks with Combined Cortisone and ACTH Therapy. These bands are related in time to the period of therapy.*

pituitary hormones. Of these, only the posterior pituitary hormone needs consideration. One may observe smooth-muscle stimulation in the form of intestinal cramps and generalized pallor immediately after injection of very large doses of ACTH, and the antidiuretic effect that occurs with repeated injections of the hormone may be enhanced by the presence of this contaminant. These changes are, of course, not observed with Cortisone therapy.

Psychic changes following ACTH and Cortisone therapy have impressed all observers. These generally take the form of euphoria, occasionally approaching hypomania, although depression has been observed. Some degree of euphoria may, of course, be attributed to the striking alleviation of pain and disability, and our experience agrees with that of Sprague et al.[35] that the degree of euphoria corresponds fairly well to the extent of the symptomatic improvement. That the euphoria may be partly due to a direct effect of the adrenal hormones

on the central nervous system is suggested by the electroencephalographic changes that they induce in patients with Addison's disease. Moreover, Sprague et al.[35] have observed typical euphoria in patients in whom these preparations failed to alter the rapidly downhill course of a fatal disease.

The mental changes associated with ACTH and Cortisone therapy have been varied but in general have appeared to represent distortions of the patient's pretreatment personality. Rarely has frank psychosis complicated the clinical picture. In our experience psychoses have been rare and have developed only in the course of diseases known to produce organic changes in the central nervous system. Thus, the etiologic role of the drug is difficult to assess, although the psychotic state has developed during a period when other systemic manifestations of the disease were improving rapidly. ACTH and Cortisone should be administered to patients with markedly unstable personalities only after thorough psychiatric appraisal and careful weighing of the possibility of inducing serious mental disturbances.

Most of the other untoward effects of ACTH and Cortisone might be predicted from the known physiologic actions of the adrenal steroids. Of these, disturbances in water and electrolyte balance are probably the most conspicuous. Retention of sodium, chloride and water occurs with great frequency during ACTH therapy; it rarely complicates treatment with Cortisone. Clinically, one observes a progressive weight gain, which presages frank edema. This phenomenon, which usually appears during the first week of therapy, may be very troublesome. It is wise, therefore, to restrict the sodium chloride and fluid intake of patients receiving ACTH. Immediately upon cessation of ACTH therapy a spontaneous diuresis occurs. Abnormal elevations in blood pressure are seen infrequently after ACTH and practically never after Cortisone.

The other commonly observed electrolyte changes consist of a hypokaliemic, hypochloremic alkalosis, which may occur independently of appreciable sodium, chloride and water retention. It is associated with easy fatigability, muscular weakness and characteristic electrocardiographic changes. Oral administration of enteric-coated potassium chloride in doses of 1 or 2 gm. three times daily will often prevent and certainly ameliorate these changes. In addition, it will tend to reduce the extent of negative nitrogen balance.[84] Because mercurial diuretics induce a large renal loss of potassium, their use is contraindicated during ACTH or Cortisone therapy unless full doses of potassium chloride are being given simultaneously.

During either ACTH or Cortisone therapy, a rise in the fasting blood sugar is almost the rule, and occasionally one may observe the development of frank diabetes mellitus. It is believed that this represents in most cases the unmasking of inadequate pancreatic islet cell reserve. Most patients in whom this complication has been observed appear to revert rapidly to normal after withdrawal of ACTH or Cortisone. Treatment, however, may be continued if necessary, provided adequate quantities of insulin are administered. Patients with pre-existing diabetes will have their diabetes markedly aggravated by ACTH or Cortisone therapy.

Hirsutism of the body, acne of the face and neck and loss of scalp hair are occasionally seen as evidences of androgenic overactivity during ACTH or Cortisone therapy. The magnitude of the change appears to be proportional to the dose of ACTH or Cortisone and the predisposition of the patients to masculinity.

Pigmentation of the skin and nails occasionally appears after prolonged administration of both ACTH and Cortisone and represents a disturbing cosmetic effect (Fig. 2). In general, inflamed areas or skin lesions are the most frequent sites of hyperpigmentation. Finally, most patients will show some tendency to develop a "Cushing-like" appearance with the typical moon face, plethora and cervical, as well as supraclavicular pads and purplish striae of the abdomen. All these changes, however, tend to disappear rapidly after withdrawal of therapy.

Careful selection of patients and close attention to details may be expected to minimize the majority of undesirable side-effects except in patients who require excessively large doses of hormone over prolonged periods to control their underlying disease. Like other potent medications, ACTH and Cortisone must be used intelligently and with respect for all their known effects.

Clinical Use of ACTH and Cortisone

ACTH as a Diagnostic Aid in the Measurement of Adrenocortical Reserve

Four-hour eosinophil response. One of the most important applications of ACTH has been its use as a diagnostic agent in the evaluation of adrenocortical function. The test in most general use at present is the four-hour ACTH eosinophil response. In this procedure a fall in circulating eosinophils has been shown to reflect increased secretion of 11,17-oxysteroids. Normal subjects respond to the administration of 25 mg. of ACTH with a 50 per cent or greater fall in circulating eosinophils. The particular merits of the test are its specificity, its simplicity and the fact that it measures not the level of adrenocortical activity at any one time but rather the *capacity of the gland to respond to further stimulation.* Hence, the test is a measure of *adrenocortical reserve.*[14] Its use as a preoperative test of adrenocortical competency has proved of value in the selection and preparation of patients for major surgery.[85]

Forty-eight hour 17-ketosteroid response. In this procedure advantage is taken of the increase in

urinary 17-ketosteroid excretion as reflecting more directly the degree of adrenocortical activation following ACTH administration. However, changes in the level of eosinophils and fasting blood sugar may also be measured. In practice, it is possible to combine the four-hour and forty-eight-hour tests. After the administration of 25 mg. of ACTH in the standard four-hour test, 10 mg. of ACTH is given every six hours during the subsequent forty-eight-hour period; 17 ketosteroid excretion is measured prior to ACTH administration and again during the twenty-four-hour to forty-eight-hour period on ACTH. The normal increase in adults is approximately 4-8 mg. per day.[86]

ACTH and Cortisone as a Diagnostic Aid in the Early Detection of the Diabetic Diathesis

The marked rise in blood sugar that follows ACTH[15] or Cortisone[35] administration to patients with diabetes mellitus, as compared to the minimal rise in normal subjects, suggests the use of these hormones as a means of unmasking early subclinical diabetes mellitus.

ACTH and Cortisone as Therapeutic Agents

On the basis of the clinical experience in the use of ACTH and Cortisone that has accumulated during a period of approximately three years, a tentative therapeutic classification of various disease states has been undertaken (Table 1).

Diseases in Which ACTH and Cortisone Appear Most Useful

The diseases included in this category may be considered in one of two groups: those in which Cortisone or ACTH supplies specific substitution therapy (Cortisone in Addison's disease and ACTH in hypopituitarism) and those in which ACTH and Cortisone may lead to permanent benefit.

Addison's Disease

Cortisone* in maintenance dosage (15 to 30 mg. daily) has greatly improved the clinical condition of many patients with severe Addison's disease. Most patients require, in addition, supplementary desoxycorticosterone acetate or sodium chloride for satisfactory electrolyte balance. The clinical improvement that follows the addition of Cortisone to a basic regimen of desoxycorticosterone is characterized by increased appetite and weight gain; increased capacity to do physical and mental work; improved capacity to sustain a prolonged fast without hypoglycemic manifestations; and correction of the abnormalities observed in the electroencephalogram and electrocardiogram.[20]

Relatively small doses of Cortisone (15 to 30 mg. daily) have produced these changes when given over a prolonged period. It is evident that patients with Addison's disease will require much larger quantities (100 to 300 mg. daily) in conditions of acute or severe stress, as during major operations.

Pellets of Cortisone have been found to be an effective method of administration over periods of three to four months.[20] A 50-mg. pellet gives off approximately 0.5 mg. per day. Patients require at least 1.0 gm. implanted as pellets for minimum maintenance Cortisone therapy in addition to a small basic requirement of desoxycorticosterone. The efficiency of Cortisone in pellet form, as contrasted with that of a similar quantity injected in divided doses, appears approximately twofold to threefold.

Treatment of patients with Addison's disease for four days with adequate doses of ACTH fails to elicit a significant adrenocortical response, whereas evidence of adrenocortical activation is readily obtained in panhypopituitarism.

*We are indebted to Dr. J. M. Carlisle, of Merck and Company, Rahway, New Jersey, for providing Cortisone for our early studies on patients with Addison's disease.

Table 1. *Preliminary Grouping of Diseases on the Basis of Response to ACTH and Cortisone Therapy.*

Diseases in Which Drugs Are Most Useful	Diseases in Which Drugs May Be Useful	Diseases in Which Drugs Are of Questionable Value	Diseases in Which Drugs Are of No Value	Diseases in Which Drugs May Be Detrimental
Addison's disease (Cortisone only)	Rheumatoid arthritis	Mental disease	Herpes simplex	Diabetes mellitus
Panhypopituitarism	Psoriasis	Multiple sclerosis	Herpes zoster and varicella	Cushing's syndrome
Functional adrenocortical insufficiency	Disseminated lupus erythematosus	Pemphigus	Poliomyelitis	Hypertension (ACTH)
Functional hypopituitarism	Dermatomyositis	Scleroderma	Progressive muscular dystrophy	Congestive heart failure
Anorexia nervosa	Periarteritis nodosa	Myasthenia gravis	Progressive muscular atrophy	Osteoporosis
Idiopathic hypoglycemia	Acquired hemolytic jaundice	Osteoarthritis	Cystic fibrosis of pancreas	Acne
Acute rheumatic fever	Vasomotor rhinitis	Paget's disease	Peptic ulcer	Hirsutism
Acute gouty arthritis	Urticaria	Tuberculosis	Sarcoidosis	
Status asthmaticus	Multiple myeloma	Pneumonia		
Serum sickness	Lymphoma	Anoxia		
Exfoliative dermatitis	Leukemia	Pernicious anemia		
Loeffler's syndrome	Nephrotic syndrome	Liver disease		
Acute inflammatory disease of eye	Ulcerative colitis	Thyrotoxicosis		
	Regional enteritis	Malignant exophthalmos		
	Pulmonary beryllosis	Glomerulonephritis		
		Cancer		
		Hypertension (Cortisone)		

Panhypopituitarism

ACTH is a specific remedy for the signs and symptoms of adrenocortical insufficiency secondary to hypopituitarism. Patients may be maintained in excellent condition with relatively small doses (5 to 10 mg. every six to twelve hours).

The response to a standard dose of 10 mg. every six hours for two to five days has been useful in differentiating primary adrenal failure from that secondary to anterior pituitary deficiency. A short course of ACTH treatment (seven to ten days) has also proved of tremendous benefit in preparing patients with hypopituitarism for surgery.[85]

In considering long-range maintenance therapy of patients with hypopituitarism there is no doubt that Cortisone will prove very useful. The indications are similar to those for whole adrenal extract. The dosage of Cortisone is identical with that for patients with moderately severe Addison's disease — that is, 10 mg. twice daily intramuscularly or 1 to 2 gm. in pellet form, implanted subcutaneously every six months.

Functional Adrenocortical Insufficiency

The use of the four-hour and forty-eight-hour ACTH tests has permitted the detection of functional adrenocortical insufficiency. In many cases in which this diagnosis has been made, patients have been acutely ill or under severe stress. Cortisone may be used with great advantage in the treatment of such patients. Its indications are similar to those for aqueous and Lipo-adrenal cortical extracts.[87] It should be given in doses of 50 to 200 mg. daily.

Functional Hypopituitarism

Adrenocortical inactivity may complicate the course of a number of diseases characterized by apathy, anorexia and wasting. Clinical studies with ACTH indicate that the low level of adrenal activity in these patients is secondary to anterior pituitary deficiency due to a hypothalamic disturbance. Patients with this syndrome exhibit a low output of 17-ketosteroids with a slow rise to normal after continued stimulation with ACTH for seven to ten days. The marked improvement in the metabolic condition of these patients following ACTH therapy often exerts a favorable influence on the course of the underlying disease.

Anorexia Nervosa

In 1942 Reiss,[88] using relatively small quantities of an active adrenocorticotrophin preparation, described the improvement in patients with anorexia nervosa.

We have observed that patients with severe anorexia nervosa often exhibit a very low 17-ketosteroid excretion, suggesting decreased adrenocortical activity. After ACTH therapy, adrenal activation has been demonstrated. Therefore, it was assumed that the low level of adrenal activity observed in these patients is secondary to anterior pituitary or hypothalamic hypofunction. After the administration of 40 mg. of ACTH daily in four divided doses to 2 such patients, a marked increase in appetite occurred at once. Seven to fourteen days of therapy resulted in over-all clinical improvement and proved of material assistance in the psychiatric treatment of these patients. These findings support the earlier observations of Reiss and indicate that the combined hormonal and psychiatric approach offers considerable promise in the care and treatment of patients with severe anorexia.

Idiopathic Hypoglycemia

The use of ACTH in idiopathic hypoglycemia has been reported by McQuarrie et al.[89] After an initial course of ACTH the patients were maintained satisfactorily on only two injections of ACTH per week. The beneficial results obtained in these unusual cases and the remarkably small quantities of ACTH required merit note. We have observed a similarly beneficial result from ACTH (10 mg. every six hours) in a patient with idiopathic hypoglycemic convulsions in whom a partial pancreatectomy had been performed with only transient benefit.

(*To be continued*)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36201

PRESENTATION OF CASE

First admission. A sixty-one-year-old American housewife was admitted to the hospital because of mild asthenia.

Nine weeks before admission the patient experienced a sudden chill followed by a temperature of 102°F. and mild prostration. A physician informed her that she had a pneumonitis in the right lower lobe, and she was treated with penicillin for two days and sulfadiazine for four days. The fever subsided promptly, but mild generalized weakness and a feeling of being below par persisted. One week later she noted the onset of a pleuritic type of pain in the right lower chest that persisted for a week and then disappeared. A chest film taken in a physician's office three weeks prior to admission disclosed a small, circular area of increased density in the right hilar region. A chest film taken six months previously had been normal. A diagnosis of atypical pneumonia was made, and a course of aureomycin therapy was instituted. This produced no clinical change, and a repeat x-ray examination three weeks after the first showed no change in the shadow within the right lung. There had been no cough, hemoptysis, night sweats or other symptoms referable to the respiratory system.

The past history was noncontributory. The patient had experienced two uncomplicated pregnancies and had undergone the menopause twenty years before admission.

Physical examination revealed a well developed, well nourished woman in no distress. The heart and lungs were clear, and no abnormalities were found.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood showed a white-cell count of 5900, with 47 per cent neutrophils, 45 per cent lymphocytes, 3 per cent monocytes, 3 per cent eosinophils, 1 per cent basophils and 1 per cent cells "resembling blasts." The hemoglobin was 13 gm. The urine was normal. No acid-fast bacilli were found on a sputum examination. An electrocardiogram was normal. A roentgenogram of the chest showed an ill defined, rounded density approximately 4 cm. in diameter lying adjacent to the midportion of the right hilus that on fluoroscopy appeared to be in the superior segment of the right lower lobe close to the fissure (Fig. 1). There was a suggestion of atelectasis immediately surrounding the lesion. The major bronchi were not demonstrably abnormal, and no definite masses were seen in the hili or mediastinum.

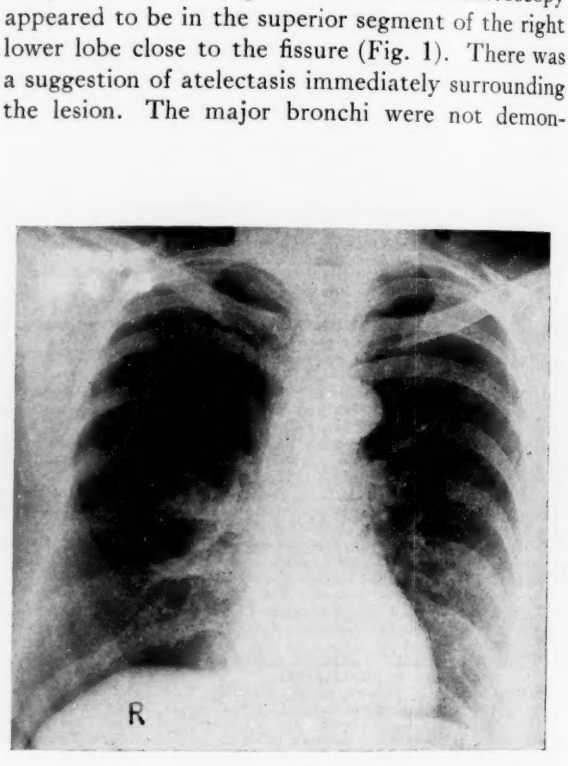

FIGURE 1. *Roentgenogram of the Chest.*
Note the hazy density lateral to the right hilar region.

A bronchoscopic examination was reported as entirely negative, with no evidence of extrinsic pressure or bronchial narrowing. A cytologic examination of the bronchial washings was negative.

Throughout the week in the hospital the patient remained asymptomatic and afebrile and was discharged for further observation.

Second admission (two weeks later). The patient remained at home after discharge, and the status remained unchanged. On readmission a chest film showed no alteration in the appearance of the lesion.

An operation was performed on the third hospital day.

Differential Diagnosis

Dr. Donald S. King*: The significant findings in the case of this sixty-one-year-old woman are the following: six months before the hospital admission, a negative chest x-ray examination; nine weeks before admission, sudden onset of chill and fever with supposed pneumonia treated with sulfadiazine and penicillin with a prompt response, pleurisy for a week and practically no symptoms after that; and, finally, three weeks before hospital admission an x-ray film showing a "small, circular area of increased density in the right hilar region." The main problem is the interpretation of the x-ray shadow. This is the problem that we face again and again, particularly when a mass chest x-ray survey is in progress.

From the story as given in the case presentation the problem sounds fairly simple. The most obvious diagnosis seems to be bronchogenic carcinoma, calling for operation. I was prepared to jump at once to this conclusion until I saw the x-ray films. I did not at first see the films that were taken outside but only those that were taken after admission. When I reviewed these hospital films I was surprised to see how little they showed and was tempted to misquote one of the most famous phrases of the recent war and say that "almost never was so much done on so little evidence." However, the films taken three weeks before the hospital entry showed a rather sharply defined, circular area of density that was certainly suggestive of tumor. If this was a tumor, it was probably not benign since the x-ray film six months before was normal. If not a tumor, can it have been an infectious process — a residuum from the supposed pneumonia? Are we dealing with a subacute or chronic pneumonitis? If so, was it one of the famous cholesterol types of pneumonitis† that have recently been described in this hospital?

Before discussing the x-ray films of the case under discussion I should like to show the slides of some films from other cases, illustrating the differential diagnosis between tumor and chronic pneumonitis. The first film is that of a man on whom I had expected to make a diagnosis of pneumonitis because of the acute onset of his symptoms. One day at 12 o'clock he was feeling perfectly well and going about his business as a contractor. At 1 o'clock he had severe right pleural pain with dyspnea and went home to bed. At 2 o'clock the temperature was 104°F., and the doctor sent him to the hospital with a diagnosis of pneumonia. He was treated for pneumonia but a few days later a chest x-ray film showed a shadow that was so rounded and sharply defined that the diagnosis of tumor had to be made. A few days later operation showed pulmonary carcinoma. The sudden onset of pain, followed by fever and chills, does not rule out bronchogenic carcinoma because infection of the tumor site may be a very early symptom. The next slide is one from a younger man, who again had the sudden onset of fever and intense pleural pain with symptoms of infection, which persisted for several weeks. It will be noted that the x-ray shadow shows a sharply defined area of density that could perfectly well represent a tumor. However, operation demonstrated not cancer but cholesterol pneumonitis. Here, then, are two somewhat similar x-ray shadows from cases in which the patient had acute onset; 1 proved to be carcinoma, and 1 chronic infection. The next slide is from a case of carcinoma, the changes in the x-ray film being due largely to the pulmonary infection secondary to the bronchial obstruction from cancer. As is often the case, the x-ray shadow is a combination of tumor and infection. The last slide shows the characteristic x-ray appearance of early carcinoma; I expected to find a small shadow of this sort in the case under discussion. In a case like this, unless there is good reason to suspect tuberculosis, one would operate expecting to find carcinoma. So much for illustrations of cases of carcinoma compared with those of pneumonitis.

For the time being I am considering only those two conditions and leaving out another group of miscellaneous possibilities.

Dr. Hanelin, will you show us the x-ray films?

Dr. Joseph Hanelin: I am showing only the posteroanterior projections because the mass is not very well seen in the oblique or lateral views. The chest films made approximately eight months before the first admission here appear entirely normal. The lungs are clear, particularly in the region where the lesion subsequently appears. The film made approximately a month before admission shows a rounded density adjacent to the right hilar shadow, which, from a set of stereoscopic films taken outside, appears to lie in the apical division of the right lower lobe. The film taken when the patient was first admitted to the hospital shows this area of density once more in the apical division of the right lower lobe, with a rather similar appearance two weeks later. The margins of the mass when first detected are rather sharply defined.

Dr. King: As I understand it, these outside films were not available when the patient was admitted to this hospital and operation was advised, so that the first film with the sharply defined border was not taken into account.

Dr. Hanelin: I do not believe the outside films were available before operation. The mass as seen in our films is a rather poorly defined one, particularly in the spot films, where the density shows no sharp margins. In the oblique projections

*Physician, Massachusetts General Hospital.

†Waddell, W. R., Sniffen, R. C., and Sweet, R. H. Chronic pneumonitis: its clinical and pathologic importance. *J. Thoracic Surg.* **18**:707-737, 1949.

around the area of involvement there are a few streaks, which are probably due to atelectasis.

DR. KING: Dr. Hanelin, have you ever seen a proved cancer with as little x-ray density as this?

DR. HANELIN: I think we have.

DR. KING: Many times?

DR. HANELIN: Not very often.

DR. KING: In our films it seems to me that we are dealing with a shadow not sharply defined and with very little density. As I said when I first reviewed the case and saw these films, I could not bring myself to consider the diagnosis of carcinoma very seriously, but I changed my opinion when I saw the outside film with the more sharply defined, rounded area. Besides, it must be remembered that with the indefinite x-ray picture there was a negative bronchoscopy and one negative examination of bronchial secretion for tumor cells. Should one advise operation on the basis of such a minimal though persistent x-ray shadow without other evidence? In many cases more than one cytologic smear should be examined since a positive finding of cells from bronchogenic carcinoma may only appear on the third or fourth trial. I assume that in this case the opinion was that the shadow had persisted and that operation was the only safe course.

Another thing, Dr. Hanelin, is there any x-ray evidence of obstructive emphysema in this case? Were films taken on inspiration and expiration to try to demonstrate partial bronchial obstruction? Sometimes this is the earliest evidence of bronchogenic carcinoma.

DR. HANELIN: I do not think that was done. I do not see any areas of emphysema in the films.

DR. KING: We must, then, admit that there is no evidence of bronchial obstruction by any test. There is negative x-ray evidence and a negative bronchoscopy. It is still possible that the tumor was in the bronchus to the superior segment of the right lower lobe and could therefore not be visualized at bronchoscopy. I remember a case in which a cancer in a bronchus to one of the basal segments could not be seen by the bronchoscope, but the diagnosis was suspected on the basis of persistent segmental atelectasis. Taking into account the sharply outlined, rounded shadow shown in the first film I am forced to accept the diagnosis of tumor and probably carcinoma.

Let us think now for a minute of other possible causes. We have been mistaken in the past and have diagnosed as tumor processes that have proved to be unusual infections such as actinomycosis and coccidiomycosis, and we have missed benign tumors and lung changes secondary to foreign bodies in the bronchi, but none of these seem to me to fit the picture.

My diagnosis, then, is bronchogenic carcinoma picked up at such an early stage that it did not produce the dense shadow in the lung field that we usually see with such a lesion.

CLINICAL DIAGNOSIS

Carcinoma of lung.

DR. KING'S DIAGNOSIS

Carcinoma of lung.

ANATOMICAL DIAGNOSIS

Tuberculoma of lung.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: It was believed in the hospital that this was tumor and that was the reason the operation was done. I have a lantern slide (Fig. 2) of the gross specimen that shows a very sharply circumscribed mass, which was about 2 cm. in diameter, surrounded by a very much larger area that can best be seen on the left-hand side. The lung tissue is grayer than normal and felt somewhat more firm and contained a little less air.

FIGURE 2. *Gross Specimen of Lung Removed at Operation.*

The microscopical sections showed that this central area consisted entirely of caseous material surrounded by giant cells and was morphologically a typical tuberculoma. It looked very much in fact like what we might expect of a primary tubercle in an infant rather than a lesion in a sixty-year-old person. The surrounding lung tissue showed a pneumonitis containing some scattered granulomas with giant cells suggesting tubercles, although there was no clear caseation, and a great deal of organized pneumonitis with fibrous plugs in many of the alveoli. There were also many phagocytes

filled with cholesterol. I spent a great deal of time examining the slides stained for tubercle bacilli, and I could not find the bacillus in any portion of the lesion.

DR. KING: You could not find even one cancer cell?

DR. MALLORY: Not a trace of a cancer cell! I think we have to make a diagnosis of tuberculosis. Unfortunately, everybody was so sure that this was a tumor that the specimen was fixed entirely, and no material was available for guinea-pig inoculation or for culture.

DR. KING: This case is fascinating. Tuberculoma never even crossed my mind in this woman at the age of sixty-one with a negative film six months before admission. If you had shown this to me in a man of twenty, I would have thought of tuberculoma first of all. In many of the tuberculomas we have seen an early diffuse process consistent with tuberculosis that has gradually concentrated into a sharply rounded shadow.

DR. MALLORY: The mass was so sharply outlined in the gross specimen that I am astounded that the x-ray film did not show a more clear focus of density.

DR. HANELIN: I think what we are visualizing is a combination of the rounded mass and the pneumonitis, which cannot be differentiated as separate processes in the films.

DR. ALLEN G. BRAILEY: Do you think it is fair to say that this was a primary tuberculous complex that had developed recently?

DR. MALLORY: I can only guess about that. It is within the limits of possibility. Against a primary lesion is the fact that the hilar lymph nodes were small although they contained miliary tubercles, but with a true primary complex one would expect rather massive involvement of the regional lymph nodes.

DR. KING: Is there any chance that this was a sarcoid type of lesion? A patient at the Cushing Veterans Administration Hospital who was sixty years old had an hemoptysis with a rounded x-ray shadow at the left base. At operation this process was said to be a granuloma consistent with sarcoid.

DR. MALLORY: I think one has to consider that possibility here, except that there was such frank caseation in the central mass that I cannot escape the diagnosis of tuberculosis.

A PHYSICIAN: At the operation when the specimen was cut, Dr. Johann Holst, of Norway, believed it was a tuberculoma, but no one else agreed with him.

DR. KING: Was this a lobectomy?

DR. MALLORY: Yes.

DR. KING: Many thoracic surgeons, once they make the diagnosis of bronchogenic carcinoma, do a pneumonectomy rather than a lobectomy. Personally, I would have hated to see this woman's entire right lung sacrificed, and I know that Dr. Churchill and Dr. Sweet often perform lobectomy and not pneumonectomy for cancer.

CASE 36202

PRESENTATION OF CASE

A fifty-nine-year-old childless widow entered the hospital because of swelling of the legs and abdomen of about two months' duration.

The symptoms started with edema of the right ankle, gradually progressing to involve the entire leg, and then the left leg and abdomen during the ensuing six weeks. The edema was constant, and redness of the legs had been noted, more on the right side. No tenderness or other signs of inflammation were noted. The patient developed dyspnea, orthopnea and shortly before admission to the hospital a nonproductive cough. During the three months prior to admission she had three episodes of bleeding from the vagina, at approximately one-month intervals, of one day's duration consisting of dark-brown blood in small amounts. Her last menstrual period had occurred seven years previously. She had noticed gradually increasing constipation, with a decrease in the caliber of the stools. Her appetite remained fairly good, and she complained of no pain other than the discomfort resulting from the abdominal distention. A complete physical examination fifteen months before entry was reported as negative, although no pelvic examination was done.

Physical examination disclosed a well developed and well nourished woman. There was no cardiac enlargement. The pulmonic second sound was greater than the aortic. A fairly harsh systolic murmur was present over the precordium. The abdomen was tense and distended, with shifting dullness. A firm, slightly tender, immobile mass, arising from the pelvis and extending above the umbilicus, was palpated. The cervix was immobile and apparently contiguous with the mass discovered in the abdomen. There was slight cervical erosion. The mass was also palpable on rectal examination. There was pitting edema of the legs, which were swollen to twice the normal size, tense and reddened, with superficial desquamation.

The temperature was 99°F., the pulse 100, and the respirations 30. The blood pressure was 180 systolic, 105 diastolic.

Examination of the blood showed a hemoglobin of 13 gm. Urinalysis revealed a specific gravity of 1.004, a ++ test for albumin and a normal sediment. An electrocardiogram was reported within normal limits.

Following admission the patient was transfused. On the second hospital day, while in the treatment room in preparation for a biopsy, she suddenly developed increased dyspnea, slight cyanosis and

grunting respirations. Oxygen was administered, and Dicumarol started. An electrocardiogram showed an auricular tachycardia of 160, with the S wave in Lead 1 not significantly increased, the Q wave variable in Lead 3 and low or isoelectric T waves in Leads 2 and 3 and in the precordial leads. A vaginal smear was doubtful, and a cervical biopsy was negative. An x-ray film of the chest revealed a large area of increased density in what appeared to be the superior segment of the right upper lobe. There was a small amount of fluid in the right pleural cavity and a suggestion of a soft-tissue mass in both peribronchial areas and in the right paratracheal area. There was some prominence of the heart in the region of the left and right ventricles. The pulmonary vascular markings were accentuated. The right leaf of the diaphragm was elevated.

During the next several days her condition gradually improved though she suffered numerous attacks of dyspnea. An electrocardiogram demonstrated a more marked inversion of the T wave in Leads 1, V_2, V_4 and AVL. Approximately twenty-five days after the original chest x-ray examination a repeat film again showed the large area of increased density in the right midlung field and the suggestion of a mass in the right paratracheal region. An x-ray film of the abdomen disclosed a soft-tissue mass in the lower abdomen filling the pelvis and extending to the level of the body of the third lumbar vertebra. The transverse colon lay above the soft-tissue mass and appeared to be displaced slightly upward by it. The pathological report of a needle biopsy stated that the specimen consisted almost entirely of rather ill defined, thin-walled cystic spaces filled with a mucinous secretion. These spaces did not have a cellular lining and there were almost no epithelial cells anywhere in the biopsy. A rare signet-ring type of cell was seen, but its identity was not definite.

The patient developed a left homonomous hemianopsia and after one month's hospitalization was discharged to a nursing home, where she died after about a month.

Differential Diagnosis

Dr. Francis M. Ingersoll*: In summary of the case history, we have a fifty-nine-year-old woman without children who had swelling of the legs, then had swelling of the abdomen and finally developed definite signs of ascites. Shortly after admission to the hospital, there was a dramatic episode, and I should like to see the x-ray films before trying to interpret that episode.

Dr. Stanley M. Wyman: The x-ray films are not good because of the patient's poor condition. There is a large area of density, which lies apparently in the superior segment of the right lower lobe. In addition, there is a second area of density lying probably in the region of the right middle lobe. The hilar and pulmonary vascular shadows are a little more prominent than usual. The mass adjacent to the trachea on the right is certainly suggestive of enlarged lymph nodes. The later films show a greater degree of density in the right paratracheal region, and there may be other shadows in the parabronchial regions. The fluid in the right pleural space at the time of the second examination had increased considerably. There is a soft-tissue density in the lower midabdomen, apparently arising from the pelvis. I do not see any gross calcification in the mass. I do not think there is much else one can say from these rather poor films.

Dr. Ingersoll: There were a few points that I expected would help us here. The first is the problem of proving that the patient had a malignant process, and I think I would say definitely that she did. There seems to be evidence in the x-ray films of paratracheal lymph nodes so that she quite obviously had metastatic disease. I would not be able to interpret whether these large masses in the chest were evidence of metastases, probably blood-borne, or whether they might possibly have been pulmonary infarcts. The fact that the masses in the chest seemed to stay is in favor of metastatic disease, although the acute episode may have been a pulmonary embolism. The abdominal films have helped us establish the diagnosis of a pelvic carcinoma with both blood-stream and lymphatic extension, but I had some hope that they would also show something that might give me a hint of the type of malignant process. There are no psammoma bodies that would suggest a papillary cystadenocarcinoma and no evidence of bone or any distinguishing mass.

I would like to discuss the etiology of the swelling of the legs. If the patient had a malignant tumor, I think it is probable that she had malig-

*Assistant in surgery, Massachusetts General Hospital.

nant invasion along the lymphatics, with obstruction, and that the edema was on that basis. That possibility seems very likely judging from the story of the fixation of the tumor and its rapid growth. The cervix seemed not to be involved particularly, and usually cervical neoplasms are the ones that metastasize to the side walls of the pelvis and produce edema but only after a much longer interval. It is my opinion that the pressure of this large tumor on the veins had been great enough to slow up the circulation and cause a thrombophlebitis in both the lower extremities. Thrombophlebitis is one of the known hazards to a woman with a tremendous fibroid; at least she runs a much greater statistical chance of having thrombophlebitis and edema in the extremities. The clinical picture certainly suggests that when the patient was put on the examining table, an embolus broke loose. I would say that the edema was caused by thrombophlebitis and that the patient had a pulmonary embolus.

Now the problem that faces us is to decide what the nature of the tumor in the pelvis was and from what it arose. Certainly, from the description I would have to say that the tumor arose from the genital tract. I think I might fairly well rule out the cervix, which showed only a little erosion, and there were a doubtful smear and a negative biopsy. The next part would be the uterus, and this clinical picture does not seem to fit in very well with any of the uterine lesions. Endometrial carcinomas slough and bleed almost continuously; they do not have intermittent bleeding occurring at one-month intervals. Certainly, if this was an endometrial carcinoma, it would have been enormous, and that would be most unlikely. It is possible that the tumor was a sarcoma of the body of the uterus. That, too, would seem unlikely with this clinic history, but with the snowballing in the chest, sarcoma certainly has to be considered as a possibility.

I suppose that this tumor was an ovarian neoplasm rather than a uterine or cervical one and that a tubal carcinoma would be very unlikely. If this was an ovarian neoplasm, how do we account for the bleeding from the uterus? Ovarian carcinomas have implants in the uterus that could account for the bleeding. Also, a functioning ovarian tumor — a granulosa-cell tumor, a thecoma or some tumor putting out estrogens — would readily explain the picture of bleeding. However, from my knowledge of these tumors, the rest of the clinical picture does not fit too well, and certainly the pathological description does not fit well.

The only hint that I have of the exact nature of the tumor comes from the pathological description, which is couched in rather ill defined language. I imagine that just means that the pathologist got a poor piece of tissue to look at. The one tumor of the ovary that I know that has the signet-ring type of cell is the so-called Krukenberg tumor — that is the metastatic tumor from the stomach to the ovary and it can reach quite a large size. We have no suggestion from the history that the patient had a carcinoma of the stomach. It is known that a similar tumor with mucus-secreting cells that form signet-ring cells can metastasize to the ovary from a tumor primary in the colon. The history of increasing constipation and decreasing caliber of the stools suggests that possibility. There was no guaiac report, and a barium enema was not done, and it is very hard to pin much on a history only. Certainly, the physicians paid very little attention to that possibility and, I think quite rightly, assumed that constipation and decrease in the size of the stool was due to the pressure of the huge mass upon the bowel rather than to a neoplasm in the bowel. The primary ovarian tumor that produces mucus is the so-called pseudomucinous cystadenocarcinoma, and that is a good possibility. If I try to narrow this down to a patient who had tumor in the pelvis and who died of pulmonary, abdominal and intracranial metastases, my first guess is a tumor metastatic from the colon to the ovary, to account for the one biopsy report we have.

Dr. James H. Currens: The reason this patient was sent to me is that she complained primarily of shortness of breath and swelling of the legs, which suggested heart disease. It soon became apparent on cursory examination that most of the trouble was in the abdomen. The episode in the hospital shortly after she had been transferred to the examining table was quite dramatic, as Dr. Ingersoll has indicated, particularly the rapidity of the pulse, which rose to between 140 and 150. The clinical impression at the time was that the patient had a pulmonary embolism. The disturbing feature was that shortly before she left the hospital she still had electrocardiographic changes that made us wonder whether or not the anterior wall of the left ventricle had been injured. The thing that interested us was the nature of this tumor. Is Dr. Ulfelder here?

DR. HOWARD ULFELDER: I saw this patient in consultation with Dr. Currens, and I also came to the conclusion that this was probably a carcinoma of the ovary. The tumor seemed to involve the uterus. I have just looked at the vaginal smear again, since I was wondering why it was called doubtful. The consideration that struck me was that the smear had a very definite estrogenic effect and a few endometrial cells and that is why it was called doubtful and not because of any cells that looked malignant. That is a very unusual finding in a patient of this age, and it makes me wonder whether or not some estrogen stimulation was going on. Of course, carcinoma of the ovary can do that without our postulating a granulosa-cell tumor. I think that the vaginal smear suggests that whatever this tumor was it might have been producing estrogen.

CLINICAL DIAGNOSIS

Ovarian carcinoma, with metastases to lung and brain.

DR. INGERSOLL'S DIAGNOSIS

Krukenberg tumor of ovary, from colon.

ANATOMICAL DIAGNOSES

Signet-ring cell carcinoma of appendix, with metastases to both ovaries (Krukenberg tumors), peritoneum, lungs, pleura and pericardium.

Coronary sclerosis, moderate.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed that the large mass in the abdomen was ovarian and when sectioned was completely replaced with gelatinous colloid material. The prosector believed that this was an example of a pseudomucinous cystadenocarcinoma or perhaps a colloid carcinoma. We looked very carefully through the entire gastrointestinal tract for a primary tumor from which this might have metastasized and found one spot that, after microscopical confirmation, proved to be the primary site, and that was the appendix. The appendix was huge and adherent to the ovarian mass. The cell type was a typical signet-ring cell — not the type seen in pseudomucinous ovarian cancers, which are columnar, but the classic round cell with the crescentic nucleus characteristic of a gastrointestinal tumor. The right ovary was the mass that was apparently felt. The left ovary was also enlarged and replaced by tumor, and there were metastases almost all over the body. The lung lesions were all metastases, and there were also metastases throughout the abdominal cavity. Most of the Krukenberg tumors, of which this is an example, metastasize to the ovary alone, and the rest of the peritoneal cavity seems to be free, but here the entire abdominal cavity was full of gelatinous tumor.

DR. ALLEN G. BRAILEY: What about the heart?

DR. CASTLEMAN: The heart showed coronary sclerosis, with moderate luminal narrowing, but there was no evidence of infarction. The tumor had compressed the inferior vena cava, the right ureter and all the pelvic veins, and I think that was the cause of the edema of the legs.

A PHYSICIAN: Was there any pulmonary infarction?

DR. CASTLEMAN: We were unable to find any evidence of infarction.

DR. CURRENS: At autopsy, grossly, there was what I considered a small area of quite significant coronary sclerosis in the lower portions of the anterior descending branch of the left coronary artery, with a definite occlusion in one short area. This location would agree with the electrocardiographic findings, which were definite for myocardial infarction.

DR. CASTLEMAN: Yes; there was a small old occlusion but no evidence of infarction.

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THE GOLD-HEADED CANE

When the president of the Royal College of Physicians of London delivered the Convocational Oration before the American College of Physicians in Boston on April 19, on the history of the Royal College, he showed to his audience at an appropriate point in the address an old-fashioned gold-headed cane.

This was in fact the very cane that, in its remarkable career of a hundred and thirty-four years of active professional service, had tapped its way from the almost elementary practice of the seventeenth century to the very threshold of modern medicine. Its story, related briefly on this occasion by Lord Moran, has been more fully told by others,* although by no one more sensitive to the meaning of the changes that it has witnessed in its faithful rounds.

The historic Gold-Headed Cane first appeared upon the medical scene in 1689 — the year of Sydenham's death — in the firm grasp of Dr. John Radcliff, of London. Radcliff, somewhat pompous and assured, physician to William and Mary and to Queen Anne, attributed his success in practice to the fact of "using all mankind ill." His financial success was certainly considerable, for he left an estate of 100,000 pounds, largely to Oxford University and St. Bartholomew's Hospital.

On his retirement Dr. Radcliff gave the cane to Richard Mead, in many ways his antithesis, for Mead, distinguished as a physician, was also learned, cultured and kindly. The cane went with him on his visits until his death in 1754, when it passed into the keeping of his former fellow student at Leyden, Anthony Askew, a man of property, a traveler and a scholar.

From Askew the cane descended to William Pitcairn, one-time president of the Royal College, brother of Major Pitcairn who fell at Bunker Hill and whose orphaned children William then adopted. David Pitcairn, a nephew, inherited the cane in 1791.

On the death of Pitcairn the younger in 1809, Matthew Baillie, who had dedicated his *Morbid Anatomy* to him, received the cane — Baillie, a nephew of the Hunters, England's first thorough student of pathology, who, "less brilliant than the Hunters, less famous than Withering or Jenner, nevertheless characterized in his person the ideal of the physician."

Gold-headed canes, however, were no longer part of the doctor's standard equipment in the nineteenth century and this one came consequently more and more to rest in Matthew Baillie's chimney corner. Here it was standing on his death in 1823, when it was presented by his widow to the Royal College of Physicians.

As the cane went to its final sanctuary in the Museum of the College, persons who were to change the whole character of the care of the sick were beginning their lives — Florence Nightingale in 1820 and Clara Barton in 1821; Pasteur in 1822; Lister in 1827. Wholly out of date as the prac-

*MacMichael, W. *The Gold-Headed Cane.* A new edition with an introduction and annotation by George C. Peachey. 195 pp. London: Henry Kimpton, 1923.

titioner's companion and staff of office, the cane remains as a symbol of the type of service that good physicians of all times have rendered. The American College may feel gratified that its recent convocation was the occasion for the Gold-Headed Cane's temporary renewal of its travels.

"THOUGH POPPIES GROW"

TWENTY-FIVE years ago the Veterans of Foreign Wars National Home for war orphans and widows was founded. Today it consists of a completely equipped 640-acre farm in Michigan, from which hundreds of children of dead or totally disabled war veterans have graduated; its honor roll contains the names of 119 members of this second generation who saw service in the war so recently ended.

The cost of maintaining the Home is largely defrayed by the sale each Memorial Day of "Buddy" poppies, made by disabled ex-servicemen. It is of interest that the first nation-wide poppy sale was conducted by the Veterans of Foreign Wars in 1922, when poppies made by women and children of the devastated areas of western Europe were offered. It was then that the seeds of forgetfulness blossomed into the flowers of remembrance.

Veterans are after all but a representative cross section of the nation's population, different only in their exposure to the circumstances that made them veterans. Most of them had no yearning for the ordeal that qualified them as "ex-servicemen," nor did those who gave "that last full measure of devotion" want to die. Perhaps the resolve can be renewed that they did not die in vain, and that the others who became permanently disabled did not make a wholly useless sacrifice.

The final lines of the famous poem by John McCrae, the Canadian poet and surgeon who died in France in 1918, may still apply:

> If ye break faith with us who die
> We shall not sleep, though poppies grow
> In Flanders fields.

MIDDLESEX EAST HUNDREDTH ANNIVERSARY

AGAIN the *Journal* is privileged to doff its cap and smite the lyre in honor of another of the district brood of the Massachusetts Medical Society that has achieved its centenarian (or centennial) status. Whichever it is, Middlesex East, following close on the heels of Norfolk, is about to celebrate its hundredth birthday, and the fellows of that district mean celebrate.

The place will be Mount Hood Golf Club in Melrose and the date June 7. Golf and other outdoor activities will open the afternoon program, after which the fellows will nurse their Charley horses at a fashion show, a showing of the Massachusetts General Hospital moving picture of the hundredth anniversary of Ether Day, and exhibits of interesting medical historical material.

After a social hour, happily named, the anniversary banquet will take place, at which Dr. Frank H. Lahey will speak on "Recent Advances in Medicine and Surgery." All members of the district society and their wives are practically required to attend.

A feature of the celebration is the publication of a commemorative booklet containing articles of historical interest, including histories of the various towns within the district, old photographic material and a copy of the district society's original charter.

AMERICAN ASSOCIATION OF THE HISTORY OF MEDICINE

ALTHOUGH the Golden West may remain the land of unlimited opportunity, a growing tendency has been noticed on the part of the recipients of its bounty to revisit the shrines that have, perforce, remained in the East.

Boston, cherishing still a variety of cultural beacons among its historic landmarks, has lately been the focal point of a number of intellectual safaris. The most recent and one of the most rigidly respectable of the national organizations that have noticed these signals in the East is the American Association of the History of Medicine, whose twenty-third annual meeting, under the presidency of Dr. Henry R. Viets, is about to take place with headquarters at the Hotel Somerset.

The first event on the program is planned for Sunday, May 21, at 2 p.m., with a meeting of the Council of the Association, followed by a reception, an informal supper and the Welch Centenary Celebration. The following day will be spent at the Boston Medical Library with the reading of miscellaneous papers and, in the afternoon, a business

meeting at which the William Osler and the William H. Welch medals will be awarded. Following this short event there will be certain visitations — to the Ether Dome of the Massachusetts General Hospital and the grave of Zabdiel Boylston — after which the spirits of the pilgrims will be revived by tea in the Faculty Room of the Harvard Medical School. The annual dinner will be held that evening.

On Tuesday morning the Association will again convene at the Boston Medical Library for a final session.

The medical fraternity of Greater Boston welcomes the American Association of the History of Medicine with its customary hospitality. It is conscious of the medical history that has been and is being made in this vicinity, and proud of its Medical Library, which has become the repository of so much priceless historical material.

The Homeopathic doctors are to have a convention on the 12th of June, in the city of Albany. — Disentery is quite prevalent in this city.

Boston M. & S. J., *May 15, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GLIDDEN — Edson W. Glidden, M.D., of Worcester, died on April 26. He was in his sixty-sixth year.

DR. Glidden received his degree from University of Maryland School of Medicine in 1907. He was medical director and superintendent of Worcester County Sanatorium and a former member of the staff of Lakeville Sanatorium, Middleboro, and was a member of the American College of Physicians and American College of Chest Physicians and a fellow of the American Medical Association.

A daughter and a sister survive.

PLUNKETT — Harold B. Plunkett, M.D., of Lowell, died on February 10. He was in his seventy-third year.

Dr. Plunkett received his degree from Kentucky University Medical Department in 1906. He was a member of the staffs of Lowell General and St. Joseph's hospitals and the Tewksbury State Hospital.

A sister and a niece survive.

SHAW — Adam E. Shaw, M.D., of Lowell, died on April 11. He was in his sixty-eighth year.

Dr. Shaw received his degree from Bowdoin Medical School in 1906. He was a member of the New England Roentgen Ray Society, and was the founder and proprietor of the Shaw Hospital.

His widow, a daughter, a son and three sisters survive.

NOTES FROM THE MEDICAL EXAMINER

IS THERAPEUTIC DECEPTION LEGAL?

To withhold from a patient the diagnosis, the extent or the dangers of his disease may be not only a matter of good therapeutics but also one of ethics and law. Most physicians view the problem of what to tell a patient suffering with a serious disease from the perspective of the patient's total personality and attempt to protect the emotionally unstable from disastrous psychic trauma. Few practitioners realize that this can lead to a dangerous schism. Doctors are torn between a therapeutic and ethical duty "to do no harm" and a legal duty inherent in the physician-patient relationship that compels complete disclosure.

One of the basic premises of Anglo-American jurisprudence is the principle of self-determination. In the law the individual is the master of his body and can expressly prohibit any therapeutic measure, even one that might be life saving. The doctor, then, cannot arbitrarily substitute his judgment for that of the patient without rendering himself liable to legal repercussions. A therapeutic course elected by the patient on the basis of the doctor's artifice and deception may lead to civil litigation because of the physician's neglect to obtain enlightened consent. This principle of law is clearly illustrated by the surgeon who operated on a young lady's hand to relieve a Dupuytren contracture. He neglected to inform her of the probabilities of a poor result. At trial, the plaintiff declared had she been aware of this fact she would never have submitted to the operation. She was awarded judgment.[1]

A patient may consult a physician for an accurate diagnosis and an accompanying prognosis. Such a consultation may give rise to a variety of legal injuries to the patient and his estate if the true nature of the disease is not disclosed. If the doctor conceals the "shock element" of his diagnosis or prognosis the patient may fail to prepare a will or trust promptly, and on his "unexpected demise" his widow can bring suit against the "humanitarian" physician. Such suppression of fact or concealment in diagnosis is a clear breach of employment and abuse of trust "sounding in tort for legal negligence." Good authority to discredit the shopworn misconception popular with many practitioners "that there is no liability for negligent diagnosis unless followed by negligent treatment" is afforded by the case in which a football player consulted an orthopedist about his injured knee. On the assurance that he could continue playing without detriment to the affected member, the star returned to the gridiron. Subsequent suit ended as disastrously for the doctor as the career did for the plaintiff.[2]

The problem appears to be slightly different when the patient has consulted the doctor for treatment.

In such cases the courts might recognize an "imperfect privilege" to withhold certain information as therapeutically justifiable. There have been no decisions directly in point. However, one Massachusetts case indirectly raised the question of the physician's right to exercise such a privilege. The plaintiff sued the doctor for malpractice. One of the allegations stated that the physician had treated her for a felon of the thumb with lymphangitis, neglecting to disclose the diagnosis. The court reasoned that such a matter should be admitted in evidence to be passed upon by the presiding judge and jury in the light of "the testimony of educated and experienced medical practitioners." Failure to allow such testimony became grounds for granting a new trial. (The doctor still lost.) Thus, there is some basis in law for holding that surgery or other treatment might be undertaken after only partial disclosure and might be legally justified (provided there was no basic or fundamental concealment tantamount to fraud). However, if an action were brought for such a suppression of diagnosis, the doctor could not suppose that the law sanctioned an absolute privilege on therapeutic grounds to conceal the truth. Rather he must realize that each case would be decided *on its merits*. There is ample authority to support the position that although the doctor has committed a technical breach of duty, the fact that such conduct was necessary to prolong or save the patient's life mitigates the damages for "improper consent."[4]

In conclusion, the decision is still a matter of medical judgment primarily, but the doctor should come as close to the truth as is defensible or plausible under the law. He must remember that when in doubt it is always best, legally and medically, to be tactfully frank. In all cases he should make an immediate and complete revelation of the facts to the closest relative. In this fashion the dichotomy between the law and good medical practice may be traversed with relative impunity.

References

1. *K. vs. Lockwood Clinic*, 4 D.L.R. 906.
2. *G. vs. H. C. Weston Co.*, 108 P2d 1010.
3. *T. and wife vs. Leach*, 65 Mass. 395.
4. *Restatement of Torts*, Sec. 920.

Woodrow W. Weiss, M.D., LL.B.
Research Fellow in Legal Medicine, Department of Legal Medicine, Harvard Medical School.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The June schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Orthopedic Clinics	Date	Clinic Consultant
Greenfield	June 1	Charles L. Sturdevant
Salem	June 5	Paul W. Hugenberger
Haverhill	June 7	William T. Green
Brockton	June 8	George W. Van Gorder
Worcester	June 16	John W. O'Meara
Fall River	June 19	David S. Grice
Springfield	June 20	Garry deN. Hough, Jr.
Pittsfield	June 21	Frank A. Slowick
Hyannis	June 22	Paul L. Norton
Lowell	June 23	Albert H. Brewster
Rheumatic Fever Clinics		**Dates**
North Reading		June 6, 13, 20, 27
Fitchburg		June 7, 14, 21, 28
Plastic Clinics		**Consultant**
Eastern Massachusetts		Bradford Cannon
	Clinics bi-monthly	
Western Massachusetts		Joseph M. Baker
	Clinics monthly	

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

PUBLIC-HEALTH AWARD

The first Lemuel Shattuck Award of the Massachusetts Public Health Association, made in recognition of distinguished service by a New Englander in the broad field of public health, was presented to Dr. Charles-Edward Amory Winslow at the sixtieth anniversary meeting of the Association at Boston University on April 25. Dr. Winslow, professor emeritus of public health at Yale University School of Medicine, is editor of the *Journal of the American Public Health Association*.

April 25 was the hundredth anniversary of the filing of Shattuck's "Report of the Sanitary Commission of Massachusetts."

CORRESPONDENCE

MISLEADING STATISTICS

To the Editor: I am writing to correct some statements in the editorial entitled "Gastric Photofluorographic Method of Cancer Detection," which appeared in the April 6 issue of the *Journal*.

Cancer of the stomach is one of the more common forms of cancer, but it certainly is not anywhere near the cause of "a third of all cancer deaths." The erroneous statement is made that gastric cancer was the cause of death of "30,000 to 40,000 in the United States as an estimate for 1949, or a third of all cancer deaths. . . ."

According to the latest census reports that I can find, cancer of the stomach and duodenum is the cause of about 1 per cent of all cancer deaths, which is much less than "a third." This is given in Bureau of Census Department of Commerce, Washington, D. C., Vol. 17, No. 6, p. 51, December 29, 1942.

It has been found here in Iowa that cancer of the stomach causes about 10 per cent of all cancer deaths.

At the Hospital at the State University of Iowa during the past ten years, the incidence of cancer of the stomach was about 6 per cent of all cases of malignant tumors seen at the tumor clinic.

It is well known that cancer of the stomach is one of the more fatal forms of cancer, but there are many other forms of cancer as fatal or more fatal than gastric cancer: cancer of the lung, prostate, pancreas, liver and its ducts and so forth, esophagus, kidney, tongue, thyroid gland and pharynx, most forms of sarcoma, melanoma, Hodgkin's disease and leukemias.

Cancer of the skin, large bowel, breast and uterus, with its cervix, are each more common than gastric cancer.

It seems to me a pity that writers of many textbooks and articles on gastric cancer prefer to use high-sounding figures that someone else has used than to give some facts that they have found in their own hospitals or cities. I should like to know where the author of the editorial obtained his figures of "a third" or 30,000 to 40,000 deaths from gastric cancer in 1949 in the United States. The editorials in the *Journal* are no doubt prepared by men whom you consider leaders in the field about which an article is written. It is such articles written by men "in high places" that lead the ordinary men to assume that cancer of the stomach is so common and kills so many people. It is truly a very serious form of cancer but why make it seem worse than it is?

FREDERICK W. MULSOW, M.D.

Linn County Tumor Clinic
Cedar Rapids, Iowa

Note: Dr. Mulsow's letter presents an excellent criticism of the gathering and dissemination of statistics. As he surmised, the "one third" was taken in good faith, from the accompanying bibliography, but without verification from sources close at hand. According to *Cancer Fact Book*, published by the Massachusetts Department of Public Health 1949, gastric cancer represented 11.5 per cent of all cancer deaths in Massachusetts in 1948, and data obtained from the same Department gave the figure of 13.7 per cent as representative of the United States as a whole. — ED.

BOOK REVIEW

Quinidine in Disorders of the Heart. By Harold Gold, M.D. 8°, cloth, 115 pp. New York: Paul B. Hoeber, Incorporated, 1950. $2.00.

D.. Gold's monograph is intended primarily as a guide for the general practitioner in the use of quinidine. It covers the pharmacology, toxic effects, therapeutic indications, dosage and application of this drug to nine types of cardiac arrhythmia. In addition its actions in angina pectoris, coronary thrombosis, thyrotoxic cardiac disorders and anesthesia and surgery are described. The combined use of digitalis and quinidine, as well as its use in children, is discussed. A useful historical bibliography is appended.

Disorders of cardiac rhythm are considered the only indication for quinidine in disturbances of the heart. It is of value in seven such arrhythmias from premature beats through ventricular fibrillation. The necessity for individualizing dosage is stressed, and as an example of tolerance the author mentions several patients receiving prophylactic daily doses of 2 to 4 gm. (30 to 60 gr.) for a period of years without ill effect.

As a general procedure in terminating an ectopic rhythm a dose of 0.4 gm. (6 gr.) every two or three hours is advised at the start. After several doses without toxic effects the dose is increased to 0.6 gm. (10 gr.) at the same rate. With increasing doses, safety is assured by observation of the patient before each dose and the taking of an electrocardiogram. Discontinuance of the drug is determined by therapeutic effect or toxic symptoms — cinchonism, gastrointestinal disorders, rarely shock and respiratory distress and prolonged auriculoventricular or intraventricular conduction. The interval between doses should not be less than two hours. Details of dosage vary with the arrhythmia. Avoidance of simultaneous use of digitalis and quinidine is advised wherever possible and "especially where large doses of both may be necessary."

The various oral, intramuscular and intravenous preparations are described. A 20 per cent solution of quinidine sulfate in propylene glycol (0.2 gm. in 1 cc.) has been found useful for intravenous and intramuscular use. The oral route is advised for most cases.

The book is recommended as a practical manual on the use of a valuable drug that is still, at times, a difficult agent to administer successfully and safely.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Modern Medicine Annual 1949: An annual volume containing the articles that appeared in the twenty-four issues of Modern Medicine *during 1948.* 12°, cloth, 779 pp., with illustrations. Minneapolis: Modern Medicine, 1949.

Studies from The Rockefeller Institute for Medical Research: Reprints. Volume 137. 4°, paper, 575 pp., with illustrations and tables. New York: The Rockefeller Institute for Medical Research, 1949.

Transactions of the American Association of Genito-Urinary Surgeons. Fifty-ninth annual meeting held at Skytop, Pennsylvania, May 12, 13 and 14, 1948. Volume XL. 4°, paper, 215 pp. Baltimore: Williams and Wilkins Company, 1949.

Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals. J. Morgan Jones, editor and publisher. 4°, cloth, 520 pp. Rutherford, New Jersey: Medical Economics, Incorporated, 1948.

Die Ermittlung des Erregungsablaufs in ungeschädigten und geschädigten Herzen durch Analyse des Elektrokardiogramms und des Vektordiagramms. By Lothar Wendt. 4°, paper, 84 pp. Berlin: Akademie-Verlag, 1949. 12.50 DM.

An Atlas of Electrocardiography. By William Dressler, M.D., cardiologist, Maimonides Hospital, in Brooklyn, consultant in cardiology, Brooklyn Hospital, and lecturer in medicine, Long Island College of Medicine; and Hugo Roesler, M.D., cardiologist, Department of Medicine, and associate professor of radiology, Temple University Medical School and Hospital, Philadelphia. 8°, cloth, 503 pp., with 439 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $14.00.

Shearer's Manual of Human Dissection. Edited by Charles E. Tobin, Ph.D., associate professor of anatomy, University of Rochester School of Medicine and Dentistry. Second edition. 4°, cloth, 286 pp., with 79 illustrations. Philadelphia: Blakiston Company, 1949. $4.50.

Acute Appendicitis and Its Complications. By Frederick F. Boyce, M.D., assistant professor of clinical surgery, Tulane University of Louisiana School of Medicine, senior visiting surgeon, Charity Hospital of Louisiana at New Orleans, and visiting surgeon, Hotel Dieu and Mercy Hospital, New Orleans. 8°, cloth, 487 pp., with 81 illustrations. New York: Oxford University Press, 1949. $8.75.

Modern Practice in Anaesthesia 1949. Edited by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A. 8°, cloth, 606 pp., with 227 illustrations. New York: Paul B. Hoeber, Incorporated, 1949. $12.50.

Surgery of Repair. By John F. Pick, M.M., M.D., clinical assistant professor of surgery, University of Illinois College of Medicine. In two volumes. 4°, cloth, Vol. I, 431 pp., Vol. II, 393 pp., with 1094 illustrations in both volumes, including 17 color plates. Philadelphia: J. B. Lippincott Company, 1949. $24.00.

The Biology of Mental Defect. By Lionel S. Penrose, M.A., M.D. With a preface by Professor J. B. S. Haldane, F.R.S. 8°, cloth, 286 pp., with 10 figures, 47 tables and 7 plates. New York: Grune and Stratton, 1949. $4.75.

Ophthalmic Medicine. By James H. Doggart, M.A., M.D. (Cantab.), F.R.C.S. (Eng.), surgeon, Moorfields, Westminster and Central Eye Hospital, ophthalmic surgeon, Hospital for Sick Children, Great Ormond Street, and examiner in ophthalmology, Royal College of Physicians and Surgeons. 8°, cloth, 329 pp., with 28 colored plates and 87 text illustrations. Philadelphia: Blakiston Company, 1949. $8.00.

The Diagnosis and Treatment of Adrenal Insufficiency. By George W. Thorn, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and physician-in-chief, Peter Bent Brigham Hospital, Boston. With the collaboration of Peter H. Forsham, M.D., M.A. (Cantab.), assistant in medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston; and Kendall Emerson, Jr., M.D., associate in medicine, Harvard Medical School, and senior associate in medicine, Peter Bent Brigham Hospital, Boston. 8°, cloth, 171 pp., with 32 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $5.50. American Lecture Series.

Vision: Its development in infant and child. By Arnold Gesell, M.D., Frances L. Ilg, M.D., and Glenna E. Bullis. Assisted by Vivienne Ilg, O.D., and G. N. Getman, O.D. 8°, cloth, 329 pp., with 72 illustrations. New York: Paul B. Hoeber, Incorporated. 1949. $6.50.

Pavlov: A biography. By B. P. Babkin. 8°, cloth, 364 pp. Chicago: University of Chicago Press, 1949. $6.00.

The Captains and the Kings Depart: And other stories. By Helen Eustis. 8°, cloth, 230 pp. New York: Harper and Brothers, 1949. $2.75.

The 1949 Year Book of Medicine (July 1948 – May 1949). Edited by Paul B. Beeson, M.D., and others. 12°, cloth, 831 pp., with 139 illustrations. Chicago: Year Book Publishers, Incorporated, 1949. $4.50.

NOTICES

ANNOUNCEMENT

Dr. C. J. McCarthy announces the removal of his office from 466 to 432 Medford Street, Somerville.

NEW ENGLAND RHEUMATISM SOCIETY

The annual meeting of the New England Rheumatism Society will be held at the Robert Breck Brigham Hospital, Boston, on Wednesday, May 24, 1950, at 8 p.m. The scientific program will be as follows:

A Comparative Study of the Effects of Pregnenolone, 21 Acetooxypregnenolone and ACTH upon Rheumatoid Arthritis and Spondylitis. H. G. Brugsch and R. Manning.

The Effects of ACTH on Blood Complement, Gamma Globulins and Fibrinogen. J. H. Vaughan, T. B. Bayles and C. B. Favour.

The Ability of ACTH and Cortisone to Alter Delayed Type Bacterial Hypersensitivity. J. B. Long and C. B. Favour.

The Life History of Juvenile Rheumatoid Arthritis. R. Barkin.

Further Experience in the Management of Osteitis Condensans Ilii. F. L. Shipp and G. E. Haggart.

Scleral Nodules (Scleromalacia Perforans) in Rheumatoid Arthritis: Clinical and pathological observations with Cortisone therapy. R. H. Talkov, F. L. Colpoys, S. Papper and R. K. Davis.

94TH INFANTRY DIVISION LECTURES

The fourteenth lecture in the series sponsored by the 94th (Bay State) Division will be held at Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, May 25, at 8:00 p.m.

Dr. Walter E. Barton, Superintendent of the Boston State Hospital and President of the Massachusetts Psychiatric Society, will speak on the subject "Recent Advances in Psychotherapy in Mental Hospitals."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will be shown during this period.

INTERNATIONAL MEDICAL MEETINGS

The United Council on World Affairs has available a list of the international medical meetings to be held during 1950, and some of those scheduled for 1951 and 1952. The Council, which is the community center for education in the field of world affairs in this area, will be glad to send mimeographed copies of this list on request. The address is 40 Mount Vernon Street, Boston. Furthermore, as the official distribution agency in this section for the State Department, the United Nations and subsidiary agencies, and numerous nongovernmental organizations in the field of world affairs, a supply of literature is available, some of which may be of particular interest to physicians. A public information center is maintained at 355a Boylston Street, where the current documents can be obtained.

DIRECTORY ISSUE OF *GRAPHICS*

The directory issue of *Graphics*, the official publication of the Association of Medical Illustrators, contains the name, address, training, professional experience and reference to major published work of each member. Other information pertaining to the profession is included. The journal, to be issued on June 1, will be available to those requiring medical illustration service, and will be sent, free of charge, upon request to the editor, Miss Helen Lorraine, 5212 Sylvan Road, Richmond 25, Virginia.

EDDIE PAINTON FELLOWSHIP IN RHEUMATIC FEVER

The School of Medicine, Western Reserve University, Cleveland, Ohio, has announced the establishment of the Eddie Painton Fellowship in Rheumatic Fever in the Department of Preventive Medicine and University Hospitals. The minimum prerequisites for the Fellowship are one year of clinical work and one year of laboratory work, or two years of clinical training.

The Fellowship carries a stipend of $3600 per year. Appointments will be made annually, but are subject to renewal. Applicants should write to Dr. John H. Dingle, Department of Preventive Medicine, School of Medicine, Western Reserve University, Cleveland 6, Ohio.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

MAY 20. The Springfield Hospital. Page 640, issue of April 20.

MAY 22 AND 23. National Research Council Committee on Human Reproduction. Page 488, issue of March 23.

MAY 23 AND 24. American Laryngological Association. Page 736, issue of May 4.

MAY 23–26. American Orthopaedic Association. Page 768, issue of May 11.

MAY 24. New England Pediatric Society. Page 736, issue of May 4.

MAY 24. New England Rheumatism Society. Notice above.

MAY 24–26. American Association of Genito-Urinary Surgeons. Page 234, issue of February 9.

MAY 25. 94th Infantry Division Lecture. Notice above.

JUNE 12–14. American Neurological Association. Page 600, issue of April 13.

JUNE 13. New England Society of Anesthesiologists. Page 735, issue of May 4.

JUNE 14–16. New England Health Institute and Massachusetts Public Health Conference. Page 768, issue of May 11.

JUNE 22–25. American College of Chest Physicians. Page 270, issue of February 16.

JUNE 23 AND 24. International Academy of Proctology. Page 768, issue of May 11.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JUNE 24 AND 25. American Academy of Dental Medicine. Page 640, issue of April 20.

(*Notices concluded on page xiii*)

NOTICES *(Concluded from page 806)*

JUNE 26–30. American Physicians Art Association. Page 428, issue of March 16.

JUNE 26–30. American Medical Association. Annual Session. San Francisco, California.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

JANUARY 31. American Academy of Orthopaedic Surgeons (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 25

THURSDAY, MAY 25
*9:00–10.00 a.m. Grand Rounds. House of the Good Samaritan.
*8:00 p.m. 94th Infantry Division Lecture. Boston University School of Medicine, 80 East Concord Street, Boston.

FRIDAY, MAY 26
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, MAY 29
*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

WEDNESDAY, MAY 31
*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.
*12:00 m. Lecture. Speaker to be announced. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.

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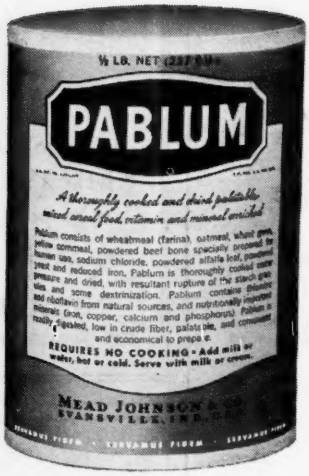
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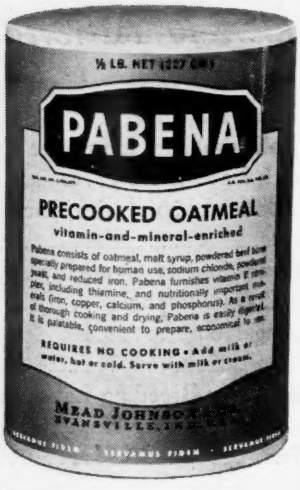
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